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Abdulla K. Salahudeen
Editors

Onconephrology

Cancer, Chemotherapy and the Kidney

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Foreword

We all recognize that major advances have been made in the treatment of patients with leukemia, lymphoma, breast cancer, prostate cancer, colon cancer, and several other malignancies over the past few decades. As a consequence, the number of survivors after a cancer diagnosis has increased from 3 million in 1971 to about 14.5 million today, which experts attribute to advancements in diagnosis, treatment, and supportive care.

The field of hematology–oncology has exponentially grown to include rationally designed biologics and small molecules that target dysregulated pathways. Though the use of these new agents has led to remarkable improvement in overall survival, some of these drugs cause nephrotoxicity. More importantly, since cancer is primarily a disease affecting older people, the renal function of patients at the time of diagnosis may be compromised due to expected decline in renal function attributed to aging cells. Given that up to a quarter of patients with a cancer diagnosis will develop new onset renal impairment, a new discipline that aims to understand and manage the challenging overlapping fields of nephrology and oncology is needed. The recent acknowledgment of the field of "Onconephrology" was heralded by the creation of the Onconephrology Forum (ONF) by American Society of Nephrology (ASN) in 2010 and the Cancer & the Kidney International Network (c-kin.org) in 2014. The publication of this textbook by Jhaveri et al., "Onconephrology: Cancer, Chemotherapy and the Kidney: A Case-Based Approach" is therefore timely and necessary. The rising awareness of this nascent scientific field will hopefully lead to improved patient outcomes.

Acute kidney injury in patients with cancer may occur by at least two mechanisms: it could arise as a complication of a particular cancer treatment (e.g., tumor lysis syndrome, drug-induced nephropathy, posttransplant related kidney diseases, surgical procedures) or be related to the neoplasm itself (e.g., renal cell cancer, anatomic obstruction due to a metastatic lesion or obstructing mass, or myeloma/amyloid affecting the kidney). It is a fact that a cancer patient that harbors or develops a kidney dysfunction has a worse prognosis than one without renal impairment.

Education about onconephrology is of utmost importance so that a true multidisciplinary approach can be developed. A growing number of treatment centers and patient support groups have started to offer onconephrology-based care programs.

More information and resources are urgently needed to help our patients understand their condition and to enhance their chances at survival.

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Preface

I am grateful and fortunate to have had great opportunities, family and friends, teachers and mentors. I graduated from Trivandrum Medical School in state of Kerala, south of India and had my initial clinical and research training in the early 80s at University of Newcastle upon Tyne under Professors David Kerr and Robert Wilkinson. My second set of clinical and research training—this time included laboratory research—was at the University of Minnesota under professors Thomas Hostetter and Karl Nath. I had an opportunity to hone my skills and establish myself as a researcher, teacher, and a clinician in the 90s while working under Professor John Bower at the University of Mississippi Medical Center. In 2006, I moved to University of Texas MD Anderson Cancer Center as the chief of nephrology section that had given me the opportunity to set up the first formal nephrology section dedicated to address the nephrology problems in cancer patients. It became immediately clear to me that most of the nephrological problems in cancer patients are unique and severe. This led me to form the first onconephrology forum of nephrologists in the USA taking care of cancer patients, which with the support of the president of ASN, professor Joseph Bonventre of Harvard Medical School became formally the ONF of ASN in 2011. This also was an opportune time in that I met in our first meeting the corresponding editor of this book, Dr. Kenar Jhaveri MD, associate professor at Hofstra North Shore–LIJ School of Medicine, trained at Memorial Sloan Kettering Cancer Hospital in cancer-related nephrology, who was equally enthusiastic and certain about the future of onconephrology. Indeed, onconephrology has become a burgeoning area in nephrology—a fertile area for learning, training, research, and improved patient care. Thanks to many nephrologists and scientists who have contributed and continued to contribute to the growth of onconephrology.

Abdulla K. Salahudeen MD, MBA, FRCP

Acknowledgments

To our trainees and patients, from whom we have gained knowledge.

To our gurus and teachers, from whom we have gained wisdom.

To our colleagues, from whom we have gained support.

To our family members, who inspire and support us for doing such contributions.

Introduction

Onconephrology: Caring for the Cancer Patient with Kidney Disease

Cancer is one of the leading causes of death and is rapidly becoming a global pandemic. Cancer patients with kidney disease have a worse prognosis with higher mortality and morbidity. The emergence of onconephrology represents a field dedicated to understanding and treating the complex renal problems that arise in cancer patients. The ASN created an ONF in 2010, setting the stage for the growth and development in this new subspecialty. Major cancer centers in the USA have started onconephrology fellowships as part of nephrology training.

A nephrologist who works closely with a hematologist and an oncologist to take care of patients with cancer is called an onconephrologist.

Acute and chronic renal insufficiency is highly prevalent in patients with cancer. Much has to be learnt on preventing acute kidney injury in the cancer patients. Chronic kidney disease and cancer are connected in several ways. Not only cancer can lead to the development of chronic kidney disease and end-stage kidney disease, but also, presence of chronic kidney disease has its associations with cancer. In this book, *Olabisi et al.* explore the causes of acute kidney injury in the cancer patients while *Sachdeva et al*. summarize the link between chronic kidney disease and cancer. In addition, there is an in depth discussion on how to manage anemia, bone disease, and hypertension in chronic kidney disease in cancer patients.

Onconephrology encompasses both the hematologic and solid cancers and their treatment-related complications that affect the kidney. Unlike general nephrology, there are several aspects of onconephrology that are unique. Onconephrology represents a milestone in the history of nephrology: A change in our nephrological perspectives.

The spectrum of fluid and electrolyte disorders in oncology patients has some important and distinct features when compared to those of the general population. *Latcha* embraces a review of all electrolyte disorders one would encounter in a cancer patient and *Gilbert et al*. explore in depth the diagnosis and management of tumor lysis syndrome. In addition, several cancers have been associated with various

glomerular diseases. *Shah* discusses that membranous nephropathy remains the most common glomerular pathology reported in patients with solid tumors. Several reports and studies in the literature suggest that treating the cancer leads to resolution of the glomerular disease.

Chemotherapeutic agents are extremely important in the treatment of malignant diseases. However, they have several side effects including nephrotoxicity which can have drastic effects on patient's morbidity and mortality. Dosing of these agents is essential in chronic kidney disease and end-stage renal disease. *Valika et al*. and *Olyaei et al*. discuss these two very important topics. Targeted therapies have emerged as excellent chemotherapy agents for many different cancers. These drugs are both specific and highly potent. Renal toxicities are now a well-recognized consequence of these therapies. *Humphreys* in his chapter explains that the renal toxicities are often cumulative, and high dose or prolonged therapy increases the risk of renal dysfunction. New drugs continue to be introduced in the market and one has to remain vigilant of their toxicities.

There is lot to be learnt from kidney diseases in cancer patients. From electrolyte disorders, tumor lysis syndrome, acute paraneoplastic glomerular diseases, radiation nephropathy, and others, there is a vast amount of clinical expertise and information that is critical to understand. In addition, it is a part of nephrology that has been lagging behind in research.

Hematopoietic stem cell transplant (HSCT) is the only cure for certain oncologic diseases. HSCT-related kidney complications remain leading cause for significant morbidity and mortality in this population. *Wanchoo et al*. tell us that the various renal toxicities following HSCT are important for the hematologist and nephrologist to understand. In addition, a separate chapter has been dedicated to radiation nephropathy by *Glezerman*.

Over the past decade, laboratory testing for monoclonal protein has improved, so has our understanding of the relationship between monoclonal gammopathies and renal diseases. *Leung et al*. expresses that from monoclonal gammopathy of undetermined significance (MGUS) to myeloma, all spectrum of plasma cell dyscrasias have been associated with renal disease. Confirming the association of kidney disease with monoclonal gammopathy is essential and treatment is geared toward elimination of the clone. Amyloidoses represent a heterogeneous group of diseases which are characterized by deposition of a pathologic proteinaceous substance in the extracellular space in various tissues of the body. The kidney is frequently affected in AL, AA, and several of the hereditary amyloidoses. *Hayes et al*. discuss the new advances in diagnosis of these entities and the treatment that has led to improvement in patient care in the past decade.

Awareness of cancer and the kidney dates back to 2005 when Eric Cohen published the first ever textbook on cancer and the kidney. Most recently, a Cancer and the Kidney International Network (C-KIN) was created in 2014 to improve patient care through better knowledge and awareness on cancer and the kidney related issues.

As nephrologists, we often are not aware of the extent of knowledge and research in the field of uro-oncology. *Salami et al*. and *Rosner* provide an in-depth review on medical and surgical management of renal cell cancer and chronic kidney disease

following nephrectomies respectively. *Abudayyeh* introduces us to the obstructive uropathy that is seen with many cancers. *Sathyan et al*. discuss a thorough review on kidney transplantation related cancers. Finally, *Soni et al*. discuss the role of palliative care in a patient with cancer and renal disease. This is an important and emerging topic of extreme importance to the onconephrologist.

It is in this backdrop, we edit this textbook on onconephrology with chapters written mostly by nephrologists or hematologist/oncologists practicing medicine and nephrology in cancer patients. Some of the topics are well-known, whereas others are less often discussed among nephrologists. In this book, we take a case-based approach to the field of onconephrology. Most of the chapters are written in an easy-to-read style with references to the latest publications in onconephrology topics. We hope this textbook would function as a stimulus or a springboard for both beginners as well as veterans in the field of onconephrology. The case-based discussion of board exam type questions challenges the reader in the subject matter. We are wishing the very best for the burgeoning field of onconephrology. Together, we dedicate this book to all the patients who suffer from both cancer and kidney disease: a devastating combination.

Kenar D. Jhaveri, MD
Abdulla K. Salahudeen, MD, MBA, FRCP

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About the Editors

Kenar D. Jhaveri MD is an associate professor of medicine in the Division of Kidney Diseases and Hypertension at the Hofstra North Shore-LIJ School of Medicine in New York. He is an attending physician at the North Shore University Hospital and Long Island Jewish Medical Center, both in New York. He is the core faculty member of the medical school and the Department of Internal Medicine. Dr. Jhaveri's clinical interests are in taking care of patients with renal complications following bone marrow transplantation and chemotherapy (onconephrology). He is one of the founding members of ASN's workgroup on onconephrology. His inspiration for onconephrology comes from his mentor and guru, Dr. Carlos Flombaum, onconephrologist from Memorial Sloan Kettering Cancer Center. His publications in onconephrology are related to glomerular diseases seen in cancer and chemotherapy, novel chemotherapy agents and nephrotoxicities and renal manifestations of myeloma. He is a columnist for the ASN Kidney News for the section called "Detective Nephron." His interest in nephrology education is vested in using creative ways of teaching nephrology to the medical students, residents, and fellows. He has also published on using social media, and other innovative tools (games, concept maps, role playing, and creative writing) to make nephrology a fun and exciting field. He has conducted numerous faculty development seminars locally to teach these techniques. He continues to have interest in novel ways of sharing information that can make an impact on all fronts: physicians, allied health staff, and the patients. He is a fellow of American Society of Nephrology, American College of Physicians, and National Kidney Foundation. He has a teaching oriented blog called Nephron Power (www.nephronpower.com) and is the Web editor for the official blog of the *American Journal of Kidney Diseases* (*AJKD*), (www.eajkd.org).

Abdulla K. Salahudeen MD, MBA, FRCP joined the Nephrology Department at the University of Minnesota in 1988 as a fellow. He has been in the academic medicine since then moving up to a full tenured professor about 15 years ago when he was at the University of Mississippi Medical Center. He maintained active research both at bench and clinical levels funded through extramural sources that included several national institutes of health (NIH) funding including an RO1 for his seminal work on the mechanism of kidney injury during cold storage. He joined the University

of Texas MD Anderson Cancer Center as the chief of nephrology in 2006 and successfully set up a new section and championed at the national level onconephrology as new and exciting subspecialty in nephrology. He was also the founding chair for the Onconephrology Forum of the American Society of Nephrology. Again, at the national level, he was the president of American Federation of Medical Research (AFMR) in 2011. He has published well over 100 peer reviewed papers, written several chapters in onconephrology.

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Chapter 1
Acute Kidney Injury in Cancer Patients

Opeyemi Olabisi and Joseph V. Bonventre

List of Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CNI	Calcineurin inhibitors
ESKD	End-stage kidney disease
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
HSOS	Hepatic sinusoidal obstructive syndrome
ICU	Intensive care unit
KDIGO	Kidney disease improving global outcomes
LIK	Lymphomatous kidney infiltration
MGUS	Monoclonal gammopathy of undetermined significance
MGRS	Monoclonal gammopathy of renal significance
MM	Multiple myeloma
MPGN	Membranoproliferative glomerulonephritis
mTOR	Mammalian target of rapamycin
NSAID	Nonsteroidal anti-inflammatory drugs

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RIFLE	Risk, injury, failure, loss, end-stage renal disease
TLS	Tumor lysis syndrome
TMA	Thrombotic microangiopathy
TTP/HUS	Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
VOD	Veno-occlusive disease

There are over 13 million patients who live with or had a history of cancer in 2010 in the USA [1]. While the overall incidence of AKI among this vulnerable group remains unknown, data from several sources suggest that it is quite high and its impact on morbidity, mortality, and cost of care is quite substantial. A Danish population-based study of 1.2 million cancer patients showed 1 and 5 year risk for AKI of 18 and 27 %, respectively [2]. On the other hand, analysis of recent data from 3558 patients admitted over a 3-month period to the comprehensive cancer center at University of Texas M.D. Anderson, Houston, Texas reported an AKI rate of 12 % of which 45 %, arguably preventable, occurred during the first 2 days of admission [3]. Studies conducted in cancer patients in the intensive care unit (ICU) by the same group showed that patients with AKI were more likely to have diminished 60 day survival, as low as 14 % (OR 14.3), and increased associated hospitalization cost by as much as 21 % [4].

Cancer is associated with many risk factors for AKI. Patients with cancer can be debilitated and may be predisposed to hemodynamic compromise associated with total or effective volume compromise. The underlying cancer itself can involve the kidney, and hence, predispose or directly cause kidney injury. Many chemotherapeutic agents can cause AKI. Additionally, AKI impacts the dosing of some chemotherapeutic agents, necessitating adjustment for diminished renal clearance. Patients with cancer who develop AKI are more likely to receive suboptimal dosing of chemotherapy [5]. Therefore, with the emergence of potent and more aggressive chemotherapeutic protocols, many of which are now accessible to previously excluded elderly patients with cancer, medical management of kidney health in cancer patients has become more complicated, and necessarily, more multidisciplinary.

This chapter reviews the epidemiology of AKI in cancer patients. The challenging issues about timely diagnosis and management are also discussed. Topics such as tumor lysis syndrome, hyponatremia, and other electrolyte abnormalities that complicate certain malignancies are discussed in detail in other chapters, and hence, are only briefly described in this chapter.

Epidemiology

How common is AKI among cancer patients? The answer depends on the subpopulation of cancer patients of interest, as well as the clinical setting, for example, intensive care unit versus general inpatient service. Also, because the incidence of AKI is dependent on how AKI is defined, comparisons are most reliable if they belong to studies that defined AKI uniformly based on RIFLE (risk, injury, failure, loss, end-stage renal disease), AKIN (acute kidney injury network), or KDIGO criteria

[6–8]. RIFLE criteria define 3 levels of AKI based on the percent increase in serum creatinine from baseline: risk (≥ 50 %), injury (≥ 100 %), and failure (≥ 200 % or requiring dialysis) [9]. Until 3 years ago, when studies of AKI in cancer started adopting RIFLE criteria to define AKI, over 35 different definitions of AKI were used in studies [3], precluding a reliable comparison of findings among studies.

In a Danish population-based study cited earlier [2], the 1-year and 5-year incidence of AKI in the overall cancer population was 17.5 and 27 %, respectively. Cancers of the kidney, gall bladder/biliary tract, liver, bone marrow (multiple myeloma), pancreas, and leukemia confer the highest risk with 1-year risk of AKI of 44, 34, 33, 32, 30, and 28 %, respectively.

In 3558 hospitalized cancer patients, 12 % of patients developed AKI. Notably, 45 % of incident AKI occurred during the first 2 days of admission [3]. By comparison, the published incidence of AKI among patients without cancer is lower (5–8 %) [10, 11]. When the same investigators examined a select cohort of 2398 critically ill cancer patients in the medical and surgical ICU with baseline serum creatinine < 1.5 mg/dL, they reported an overall incidence of AKI to be 12.6 % [4]. This incidence is lower than the historically reported incidence of 13–42 % [12–14]. When the analysis was limited to cancer patients admitted to the medical ICU only, the incidence of AKI was 21 %. The relatively lower overall incidence of AKI in this study was multifactorial: cancer patients with significant baseline CKD were excluded, and the study included a large proportion (58 %) of patients admitted to the surgical service (many electively), who might be expected to have a lower risk of AKI as they are not as acutely ill as patients admitted to medical ICUs.

In the study mentioned above, the cancers associated with the highest incidence of AKI in the ICU setting were hematologic malignancies such as leukemia, lymphoma, and myeloma, with combined AKI incidence of 28 % [4]. This incidence was notably lower than that reported by another recent prospective study that measured the incidence of AKI (defined by RIFLE criteria) among ICU patients with newly diagnosed high-grade hematological malignancies (non-Hodgkin lymphoma, acute myeloid leukemia, acute lymphoblastic leukemia, and Hodgkin disease) who did not show preexisting CKD. The incidence of AKI in this study was 68.9 % [5].

Not surprisingly, among patients with hematologic malignancies, those treated with hematopoietic stem cell transplantation (HSCT) have the highest risk of AKI, with the risk varying with the type of HSCT. Myoablative allogenic HSCT is associated with a higher risk of AKI (> 50 %) [15–19] than nonmyoablative allogenic HSCT (29–40.4 %) [18–20], presumably because the former involves use of a more toxic conditioning regimen. Also, because autologous HSCT is not complicated by graft versus host disease (GVHD), and does not require use of calcineurin inhibitors, it is associated with a relatively lower incidence of AKI (22 %) compared to allogenic HSCT [21].

Four main points may be deduced from these studies: (1) the incidence of AKI among hospitalized cancer patients is higher than that of patients without cancer; (2) acutely ill cancer patients admitted to the ICU have yet higher risk of AKI; (3) some cancers are associated with higher risk of AKI than others; and (4) treatment

with HSCT, especially myeloablative allogenic HSCT, further raises the risk of AKI associated with malignancies.

Causes of AKI in the Patient with Cancer

The etiologic framework of AKI in the patient with cancer is similar to that of noncancer patient in which causes of AKI can be categorized based on the location of the culpable "lesion" as prerenal, intrinsic renal, and postrenal causes (Fig. 1.1). As with AKI in noncancer patients, this approach lends itself to easy application. Although this is a useful construct, certain etiologies of AKI may not neatly fall exclusively into one of the three categories. For instance, some etiologies, such as nephrotoxicity associated with calcineurin inhibitors can be due to both prerenal and intrinsic renal effects due to their effects on vasoconstriction of prerenal and intrarenal vasculature as well as their direct epithelial cell toxicity. Yet, other causes of AKI, such as intravascular hypovolemia may initially lead to prerenal AKI. If the renal ischemia persists, however, it may ultimately lead to tubular injury and necrosis, which moves the etiology into the "intrinsic renal" category. Furthermore the etiology of AKI in cancer patients is often multifactorial.

Prerenal Causes

Sepsis and hypoperfusion are commonly reported causal etiologies of AKI in patients with cancer [22, 23]. Sepsis is an example, however, of a combination of prerenal and intrinsic renal AKI, since sepsis has multiple effects on the tubular epithelial cell as well as the endothelial cell. Sepsis is a common cause of hypovolemia via capillary leak, especially among ICU cancer patients. Cancer patients are prone to developing cancer- or chemotherapy-related conditions that ultimately result in renal hypoperfusion. In a recent study of patients with hematologic malignancies, AKI was caused by renal hypoperfusion in 48.2 % of cases [5]. True intravascular volume depletion often results from diarrhea, vomiting, decreased oral intake, and overdiuresis. Additionally, effective circulating volume declines in the setting of malignant ascites and pleural effusions. Nonsteroidal antiinflammatory drugs (NSAID) and angiotensin converting enzyme inhibitors (ACEI) impair the renal vascular autoregulatory systems, thereby acting synergistically with hypovolemia to create a renal hypoperfused state.

Hypercalcemia, which occurs in 20–30 % of cancer patients over the course of their illness [24], causes vasoconstriction and the associated augmented natriuresis leads to volume depletion. Renal vein thrombosis and impaired cardiac function, for example, due to pericardial effusion, also can contribute to renal hypoperfusion.

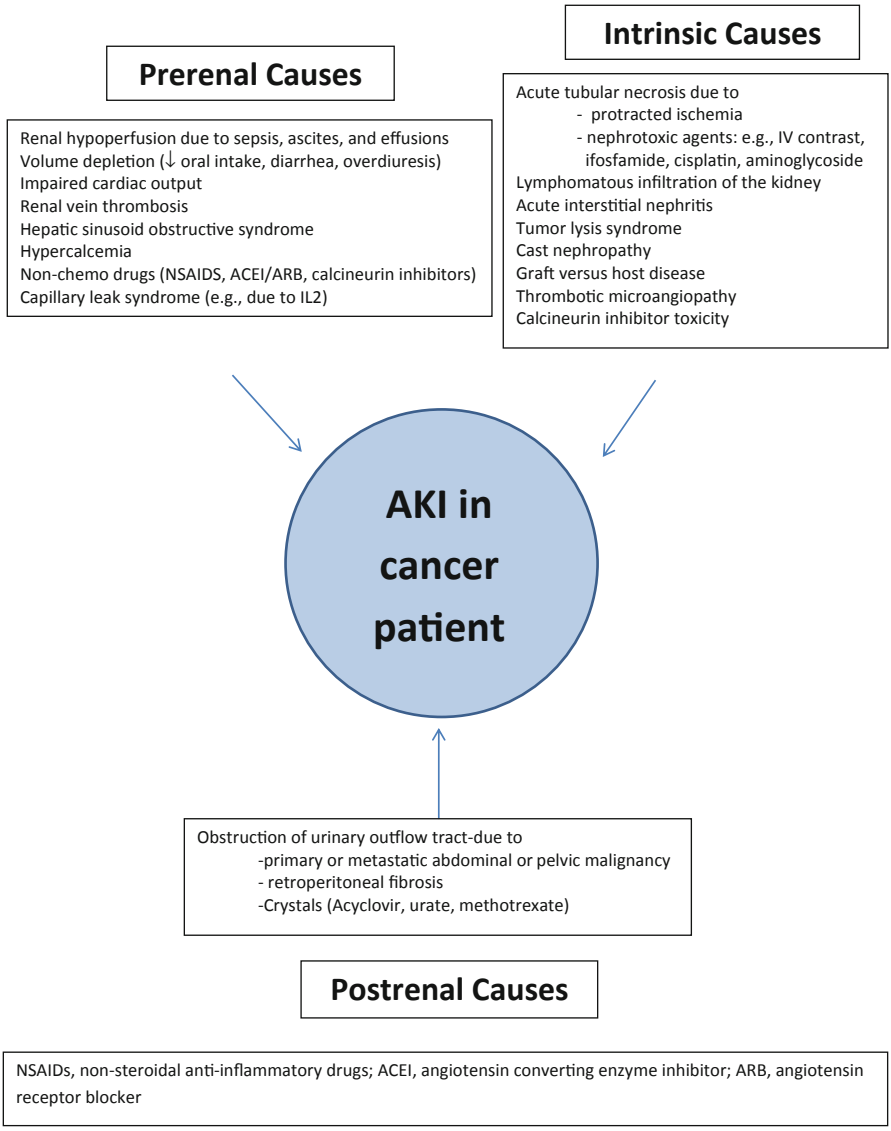

Fig. 1.1 Causes and syndromes leading to acute kidney injury in cancer patients

Likewise, hepatic sinusoidal obstructive syndrome (HSOS), also known as hepatic veno-occlusive disease (VOD), results in "hepatorenal-like" physiology, with impaired renal perfusion.

Case #1
A 56-year-old male with renal cell carcinoma receives an mTOR inhibitor for metastatic disease. Over 2 weeks, a rapid rise in serum creatinine is noted. Urinalysis reveals no red blood cells, white blood cells, or blood. Complete blood count shows a slight decrease in platelet count and no eosinophilia. Granular casts are noted on examination of his urinary sediment. What is the most likely finding in the kidney biopsy?
a. Thrombotic microangiopathy
b. ATN
c. Acute interstitial nephritis
d. FSGS

Intrinsic Renal Causes

Acute tubular necrosis (ATN) is a common, nonspecific endpoint of renal tubular injury. Persistent ischemia from any etiology, and nephrotoxins, including cytotoxic chemotherapy and nephrotoxins released during tumor lysis, result in acute tubular injury. The list of nephrotoxic agents that cause toxic ATN is long. The most common chemotherapeutic agents that have been associated with ATN are presented in Table 1.1. In addition, an entire chapter in this book is dedicated to chemotherapy agents and kidney disease for further details. This list continues to expand to include some ever emerging new chemotherapeutic agents such as inhibitors of mammalian target of rapamycin (mTOR) [25]. It is also important to recognize that there can be significant ischemia to the kidney even though total renal blood flow is preserved if the distribution of renal blood flow leaves important regions of the kidney, such as subsections of the outer medulla, underperfused [26].

It is important to recognize that ATN is a diagnosis, which depends upon evidence that there is necrosis of epithelial cells. ATN is not a clinical diagnosis. The diagnosis can be made noninvasively, however, by observing clear evidence for tubular cell necrosis in the urine sediment. The clinical entity associated with ATN is AKI. The diagnosis of ATN is based on the presence of "muddy brown" or granular casts on urine microscopy. Biopsy is not routinely performed to diagnose ATN, but characteristic findings on renal biopsy include tubular cell degeneration, loss of brush border, apoptosis, and evidence for a reparative response by the tubule, for example, mitotic figures. Immunohistochemical staining shows notable increase in cell cycle-engaged cells and derangement of tubular Na^+, K^+-ATPase expression. There are no radiographic modalities for specifically diagnosing ATN in the clinical setting. As the current diagnostic methods rely on late markers of ATN, diagnosis, and, in turn, treatment of ATN is often delayed. There are ongoing efforts to optimize the use of biomarkers that could diagnose ATN noninvasively, sensitively, and early in the disease process [27–29]

Table 1.1 Chemotherapeutic agents associated with AKI and other forms of kidney injuries

Chemotherapeutic agent	Mechanism of AKI	Clinical presentation	Prophylaxis	References
Azacytidine	Proximal and distal tubular injury	Mild Fanconi syndrome, and polyuria	None established. Self-limiting	[112]
Bisphosphonate (pamidronate, zoledronate)	Acute tubular injury and FSGS	AKI	Avoid use of Zoledronate in patients with CrCl < 35 ml/min. In those patients, reduced doses of pamidronate and ibandronate can be given	[113, 114]
Bevacizumab (and other VEGF inhibitors)	Glomerular endothelial injury, causing TMA; disruption of epithelial slit diaphragms	Proteinuria, HTN, TMA, and AKI	None established	[115, 116]
Cetuximab and panitumumab (monoclonal antibody against EGF receptor)	Deactivation of magnesium channel, TRPM6	Magnesium wasting	None established	[117, 118]
Cisplatin	Toxic damage to renal tubule	AKI, magnesium wasting	Volume expansion, amifostine	[72, 119]–[122]
Cyclophosphamide	Increased ADH activity	Hyponatremia	None established Self-limiting after discontinuation of drug	[76]
Gemcitabine (cell cycle-specific pyramidine antagonist)	TMA	HTN, TMA, proteinuria, and AKI +/− Edema	None established	[123]
Ifosfamide	Proximal +/− distal tubular injury	ATN (often subclinical); Type 2 RTA with Fanconi syndrome; severe electrolyte disarray; nephrogenic diabetes insipidus	Moderate-severe nephrotoxicity generally occur with cumulative doses 100 g/m^2 Avoid concurrent use of cisplatin	[78, 124]
Interferon (alpha, beta, or gamma)	Podocyte injury resulting in MCD or FSGS	Nephrotic syndrome, AKI		[125, 126]

Table 1.1 (continued)

Chemotherapeutic agent	Mechanism of AKI	Clinical presentation	Prophylaxis	References
Interleukin-2	Renal hypoperfusion due to capillary leak, renal vasoconstriction	Hypotension, proteinuria, pyuria	None established	[127, 128]
Methotrexate	Nonoliguric AKI	Tubular obstruction by precipitation of methotrexate and 7-hydroxy-methotrexate	Volume expansion; urinary alkalization; leucovorin rescue; dose reduction for GFR < 10–50 ml/min	[94, 129]
Mitomycin C	AKI	TTP and HUS (associated with cumulative dose > 60mg	None established	[83, 130]
mTOR inhibitors	AKI	ATN, proteinuria	None established	[25]
Nitrosoureas	Glomerular sclerosis and tubulointerstitial nephritis	Insidious, often irreversible renal injury	Volume expansion	[131, 132]

AKI acute kidney injury, *FSGS* focal segmental glomerulosclerosis, *CrCl* creatinine clearance, *TMA* thrombotic microangiopathy, *HTN* hypertension *ATN* acute tubular necrosis

Case #1 Follow-Up and Discussion
The patient presented previously, shows ATN in the presence of a urine sediment with granular muddy brown casts. As noted above mTOR inhibitors have been reported to cause ATN as well as proteinuric renal diseases.

It is not always the case that the correction of renal ischemia, resolution of septic shock or removal of an offending nephrotoxin, leads to complete resolution of ATN. The initial insult may result in a repair process that is incomplete and maladaptive. This may not be initially apparent, but is supported by the higher risk of future CKD [30–32]. Therefore, prevention of ATN should be the goal. Prophylaxis against ATN is aimed at hemodynamic optimization, intravascular volume expansion with crystalloids or diuresis, to augment cardiac filling and renal perfusion and reduce intrarenal concentrations of nephrotoxic agents. The approach also involves avoiding sepsis and treating the cancer before it has an impact on renal function either directly or indirectly. Once AKI is established, treatment is aimed at optimizing hemodynamic support, treating sepsis if it is present and withdrawing or reducing the dose of the nephrotoxic agent if possible.

Lymphomatous Kidney Infiltration (LIK)

Lymphomatous kidney infiltration is common, albeit underdiagnosed, among cancer patients. Its incidence ranges from 6 to 60 % in autopsy series [33]. In the largest autopsy case series comprising 696 cases of malignant lymphoma, LIK was found in 34 % of cases, although only 14 % were diagnosed before death. Although kidney infiltration was bilateral in the majority (74 %) of cases, it was associated with acute renal failure only in 0.5 % of cases [34]. It must be considered however that the definition used for acute renal failure in 1962, when this paper was published, is very different from the one used today for AKI. This supports the observation that LIK is a common complication of hematologic malignancies, but may not be a common cause of severe AKI in these patients.

The reason for LIK underdiagnosis is multifactorial. Most patients with LIK have no clinical renal manifestations [33], and when present, clinical manifestations such as flank pain, hematuria, abdominal pain, palpable mass, hypertension, and subnephrotic range proteinuria—are not specific to LIK [33, 34]. While lymphoma cells may be present on urinalysis they frequently go unnoticed. Common findings on urinalysis are mild proteinuria, few red blood cells, white blood cells, and granular casts. The sensitivity of radiographic diagnosis is also poor with diagnosis of LIK by computed tomography imaging in the range 2.7–6 % [35]. While LIK is almost always diagnosed by renal biopsy [36], a biopsy is not frequently obtained because cancer patients with LIK often have nonrenal cancer complications to which their renal insufficiency may be ascribed. Concurrent coagulopathy in the acutely ill cancer patient is often seen as a relative contraindication to renal biopsy. A kidney biopsy is pursued when the diagnosis of LIK would prompt initiation or modification of chemotherapeutic agents.

The mechanism of LIK-induced AKI is not completely established. Since tubules and glomeruli usually appear morphologically normal on biopsy, it has been proposed that interstitial and intraglomerular pressure elevation due to lymphocytic infiltrations of these compartments is the underlying mechanism of the AKI [33, 36]. Proponents of this mechanism also point to improved renal function with chemotherapy being supportive of this hypothesis. Complete renal recovery to baseline function is not frequent [37]. Management of LIK is focused on treatment of the underlying malignancy.

Myeloma Cast Nephropathy

Renal impairment affects 20–40 % of newly diagnosed patients with multiple myeloma (MM) [38, 39]. Some case series report that up to 10 % of patients with newly diagnosed multiple myeloma have AKI severe enough to warrant dialysis [39, 40]. While cast nephropathy is not the sole etiology of AKI in patients with multiple myeloma, cast nephropathy is the most common finding on renal biopsy, found in 41 % patients biopsied with monoclonal gammopathies [41]. In this cohort,

AL-amyloidosis was found in 30 %, light chain deposit disease in 19 %, tubulointerstitial nephritis in 10 %, and cryoglobulinemic kidney lesions with MM in 1 patient. Factors that promote cast formation and AKI in myeloma include dehydration, delivery of high burden of serum-free light chains to the distal nephron, acidic urine, concurrent use of furosemide or NSAIDs, hypercalcemia, and intravenous contrast use [42, 43].

The majority of studies show that AKI in patients with MM is associated with increased morbidity and mortality [44–46]. By contrast, in one case series, when adjusted for the stage of MM, renal failure had no impact on survival [47]. It was suggested that, as renal function is closely correlated with myeloma cell mass [48], the correlation between renal impairment and increased mortality may be more reflective of the burden of MM than that of renal impairment per se [49]. It is noteworthy that in other malignancies, as in noncancer patients, AKI correlates with increased morbidity and mortality. It will be surprising if this is not the case in MM as well. Treatment of renal disease associated with myeloma is discussed elsewhere in this book.

Case #2
A 56-year-old male is noted to have subacute rise in serum creatinine and development of hematuria and proteinuria. Serological workup is negative but serum-free light chains revealed an abnormal ratio of elevated kappa to lambda of 9 (serum creatinine is 1.5 mg/dl). A bone marrow study revealed MGUS (monoclonal gammopathy of undetermined significance) with only 4 % IgG kappa plasma cells. A kidney biopsy revealed a MPGN pattern of injury with immunofluorescence positive for IgG kappa. How do you proceed with treatment?

a. Start steroids for treatment of MPGN
b. Treat underyling B cell clone in the bone marrow and treat this as monoclonal gammmopathy of renal significance
c. Repeat the bone marrow
d. No treatment till plasma cells are > 10 % and a diagnosis of myeloma is made.

Membranoproliferative Glomerulonephritis Secondary to Monoclonal Gammopathies

The spectrum of renal injury associated with monoclonal gammopathy is broad [50]. While, as stated above, the majority of kidney diseases associated with monoclonal gammopathies are due to the deposition of light chains [51], it is becoming increasingly recognized that an immune complex glomerulonephritis can occur. This is characterized by subendothelial and mesangial immune complex deposition and is

an underappreciated cause of kidney injury caused by monoclonal gammopathies both in native kidneys [52] as well as in renal allografts [53].

Case #2 Follow Up and Discussion
In a large biopsy case series, the incidence of monoclonal gammopathy-associated MPGN was higher than hepatitis-associated MPGN and was nearly equivalent to the incidence of myeloma kidney [52]. This study highlights the important point that MPGN is associated with a wide spectrum of plasma cell and lymphoproliferative disorders, ranging from multiple myeloma at one extreme and MGUS at the other end of the spectrum. Because many patients with MPGN have underlying monoclonal gammopathy, there is a need for careful investigation before using the diagnostic label of MGUS—because what may appear as "undetermined significance" may be causally associated with MPGN. Similarly, before diagnosing idiopathic MPGN, a full work-up for gammopathies—including serum electrophoresis—should be undertaken. Patients with monoclonal gammopathy have an incidence of MPGN recurrence that is twice of that seen in patients without monoclonal gammopathy (66.7 vs. 30 %) [54]. Because kidney biopsies are generally delayed—especially, when anti-GBM or pauci immune diseases are not the suspected etiology of AKI, it is unknown how frequently AKI is the initial presentation of MPGN. It is likely, however, that more MPGN cases present initially as AKI than appreciated. Awareness of this possibility will increase the likelihood of early diagnosis and treatment. Based on the above discussion, the patient in case 2 should be treated promptly for the underlying B cell clone that is present in the bone marrow and affects the kidney. This is MGRS (monoclonal gammopathy of renal significance) and not MGUS anymore. Watchful waiting might lead to ESKD. Since there appears to be a secondary cause of MPGN in this case, steroids alone will not be sufficient. The correct answer is b.

Tumor Lysis Syndrome (TLS)

TLS is the most common oncologic emergency [55] with incidence as high as 26 % in high-grade B-cell acute lymphoblastic leukemia [56]. TLS results from rapid release of intracellular contents of dying cancer cells into the bloodstream either spontaneously or in response to cancer therapy. It is biochemically characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Cardiac arrhythmias, seizures, and superimposed AKI are common clinical presentations. The pathophysiology of TLS-mediated AKI involves intratubular obstruction and inflammation by precipitation of crystals of uric acid, calcium phosphate and/or xanthine. Preexisting renal dysfunction favors intratubular crystal precipitation [57]. Consensus recommendations for TLS prophylaxis include volume expansion for

all risk groups, use of allopurinol in medium- and high-risk groups, and use of recombinant urate oxidase (rasburicase) in high-risk groups [58]. Care should be taken, however, with use of this agent, which converts uric acid to allantoin, carbon dioxide, and hydrogen peroxide, since the latter can lead to methemoglobinemia and hemolytic anemia in individuals with glucose-6-phosphate deficiency. Utility of diuretics and urine alkalization are variable and their efficacy is debatable [58]. A chapter of this book has been devoted to TLS.

AKI Following Hematopoietic Stem Cell Transplantation (HSCT)

AKI is a common and consequential complication of HSCT. Causes of AKI following HSCT are divided into early onset (< 30 days) or late onset (> 3 months) [42]. Early AKI is commonly caused by sepsis, hypotension, and exposure to nephrotoxic agents [42]. Moreover, TLS and hepatic sinusoidal obstruction syndrome (HSOS) are also causes of early AKI with onset within 30 days of HSCT. Late onset AKI is often due to either thrombotic microangiopathy (TMA) or calcineurin inhibitors (CNIs) toxicity [15, 42].

The incidence of AKI varies according to the type of HSCT: AKI is less frequent after autologous HSCT when compared to allogenic HSCT because the former patient is spared the nephrotoxicity of CNI, which is used for treating GVHD prophylaxis in the latter. Similarly, a nonmyeloablative conditioning regimen is associated with lower risk of AKI than a myeloablative conditioning regimen because the former involves use of a less intense regimen and lower risk of HSOS.

The diagnosis of TMA is often delayed because many of its characteristic features— anemia, thrombocytopenia, AKI, elevated serum LDH—are nonspecific and are common findings in cancer patients post-HSCT in the absence of TMA. The presence of schistocytes and hypertension can be helpful but alone are not sufficient for a definitive diagnosis. A high index of suspicion is required for a diagnostic workup for TMA to be initiated. If a biopsy is done, it often shows mesangiolysis, GBM duplication, glomerular endothelial swelling, tubular injury and interstitial fibrosis [42, 59]. Except for atypical cases or situations where the management course would be altered, a kidney biopsy is often not required. Management of HSCT-associated TMA is supportive, and often involves discontinuation of CNIs—because CNIs are known to increase the risk of HSCT-associated TMA [42, 60].

Hepatic sinusoidal obstruction syndrome (HSOS) is characterized by sinusoidal and portal hypertension that result from radio-chemotherapy-induced endothelial cell injury of hepatic venules [60]. AKI develops in nearly 50 % of HSCT patients who develop HSOS [15, 42]. The pathophysiology of HSOS-associated AKI is similar to hepatorenal physiology, characterized by fluid-retention, sodium retention, low urinary sodium, peripheral edema, weight gain, and usually bland urine sediment. Notably, more than 70 % of patients with HSOS will recover spontaneously with only supportive care—managing sodium and water balance, augmenting renal perfusion, and relieving symptomatic ascites with repeated paracentesis [42, 61]. For details on HSCT-associated renal disease, refer to a related chapter in this book.

Chemotherapy with Nephrotoxicity

Chemotherapeutic agents that are associated with nephrotoxicity are listed in tabular form in Table 1.1. These chemotherapeutic classes include cytotoxic, platinum-containing agents, alkylating agents, antitumor antibiotics, and antimetabolites. Detailed discussions of these chemotherapy agents are presented in another chapter of this book. Here we review some general features of their causal relationship with AKI.

Calcineurin Inhibitors (CNIs) Toxicity In patients who have undergone allogenic hematopoietic stem cell transplant, CNIs (cyclosporine and tacrolimus) are used for prevention of graft versus host disease (GVHD). Both of these medications cause AKI by causing renal vessel vasoconstriction and direct tubular toxicity, resulting in reduced GFR. The AKI is usually reversible with dose reduction. CNIs are also known, however, to cause progressive, irreversible CKD associated with tubule-interstitial fibrosis in a striped pattern along medullary rays. These agents have also been implicated as risk factors for TMA [42, 62].

Nephrotoxicity Associated with Platinum-Containing Agents Platinum-based chemotherapeutic agents are important anticancer therapies. Cisplatin, the founding member of the group, is a simple inorganic compound consisting of an atom of platinum surrounded by chloride and ammonium atoms in cis position. Since its approval by the US Food and Drug Administration in 1978 as a therapeutic agent, it has become one of the most frequently used chemotherapeutic agents, especially against solid tumors [63]. Its clinical use is limited by major toxicity (nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression) of which nephrotoxicity is the most serious and dose limiting [64]. One third of patients treated with cisplatin develop renal impairment within days following the initial dose [65]. The kidney's vulnerability to cisplatin toxicity is thought to be due to its function as the principal excretory organ for platinum [66]. Because of its low molecular weight and uncharged state, cisplatin is freely filtered through the glomerulus as well as secreted by tubular epithelial cells [67], and accumulates in both the proximal and distal tubules where it exerts its nephrotoxic effects, especially at the S3 segment of the proximal tubule lying in the outer medulla [68, 69].

Clinically, AKI caused by cisplatin is often nonoliguric and is characterized by tubular dysfunction, inability to concentrate urine, and inability to reabsorb magnesium—seen in $> 50\,\%$ of patients treated with cisplatin [70]. Glucosuria, aminoaciduria, hypokalemia, hyponatremia, hypocalcemia, and hypochloeremia may also be present as additional evidence of tubular dysfunction [67]. Severe salt wasting can result in orthostatic hypotension and/or incomplete distal tubular acidosis in some patients [71]. The underlying pathophysiology of cisplatin-induced AKI is attributed to four types of injuries: (1) tubular toxicity, due to direct injury to epithelial cells; (2) vascular damage to small and medium size arteries, due to decreased renal blood flow because of obstruction and/or inflammation; (3) glomerular injury; and (4) interstitial injury, typical of long term cisplatin exposure [66]. The tubular injury is attributed to a complex, interconnected multifactorial process including enhanced

accumulation of cisplatin via transport-mediated process [69], metabolic conversion of cisplatin to a nephrotoxin [72], DNA damage [73], dysregulated epithelial cell transporters activity, mitochondrial dysfunction [74], oxidative and nitrosative stress [75], as well as activation of proinflammatory signaling pathways such as NF-kB and MAPK pathways [66].

Risk factors of cisplatin nephrotoxicity include patient-related factors and drug related factors. The most important patient-related factors include age (especially, greater than 60 years old), female gender (have 2-fold higher risk as men), African-American race, malnourished/dehydrated state, preexisting renal insufficiency (GFR < 60 ml/min/1.73m^2), and concomitant administration of nephrotoxic agents, reviewed in [66]. Cisplatin doses higher than 50 mg/m2, long-term exposure to cisplatin, as well as repeated exposure, are all associated with cisplatin-induced AKI [66, 68]. Newer platinum agents such as oxaliplatin, carboplatin, and nedaplatin appear to be less nephrotoxic than cisplatin. These are alternative agents, especially for patients at relatively high risk for AKI.

Nephrotoxicity Associated with Alkylating Agents Ifosfamide and cyclophosphamide are used in conjunction with other chemotherapy to treat metastatic germ cell tumors and some sarcomas. Ifosfamide is a synthetic isomer of cyclophosphamide. Hemorrhagic cystitis is the predominant toxicity of both agents. Hyponatremia due to increased antidiuretic hormone activity is the primary renal-related adverse effect of cyclophosphamide [76], and it reverses promptly upon discontinuing the agent. Moreover, clinical nephrotoxicity is seen in up to 30 % of cases when Ifosfamide is used [77]. Subclinical glycosuria, evidence of proximal tubular toxicity, is reported in 90 % of patients in a pediatric study [78]. The nephrotoxicity of ifosfamide is attributed to the 40-fold greater quantity of chloroacetaldehyde produced from its metabolism relative to cyclophosphamide [77]. In vitro studies suggest that chloroacetaldehyde directly injures the proximal tubule causing type 2 renal tubular acidosis with Fanconi syndrome [79, 80]. While moderate declines in GFR may be seen, significant loss of GFR is not a major feature of ifosfamide AKI except if there is a concomitant use of cisplatin. The timing of the tubular dysfunction is variable [81], and it is generally reversible. However, in some cases decline in glomerular and tubular function may continue even after cessation of ifosfamide [78]. Risk factors for ifosfamide-induced AKI include cumulative dose (moderate to severe nephrotoxicity tend to occur with cumulative dose > 100 g/m2), age < 4–5 years old, and prior or concomitant cisplatin therapy [78, 82]. Therefore, limiting cumulative dose and avoiding concurrent use of cisplatin is a corner stone of preventing ifosfamide-induced nephrotoxicity.

Nephrotoxicity Associated with Antitumor Antibiotics Mitomycin is an antitumor antibiotic with well-characterized renal toxicity. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) is the most common nephrotoxicity associated with mitomycin C [83, 84]. The overall incidence is ranges from 2 to 28 % of patients depending on the cumulative dose [85, 86]. Renal failure due to mitomycin occurred in 2, 11, and 28 % of patients receiving cumulative doses of 50, 50–69, and > 70 mg/m^2, respectively in one series [85]. Direct endothelial

injury is the presumed inciting event [86, 87]). In a rat model of mitomycin-induced TTP/HUS, evidence of endothelial injury was obvious as early as 6 h following mitomycin infusion, and a clear picture of thrombotic microangiopathy has developed by day 7 postmitomycin infusion. However, in humans, the onset of clinical evidence of TTP/HUS is typically delayed more than 6 months following exposure to mitomycin [87]. The basis for the difference in the time of onset between animal model and human is unknown. Treatment with plasmapharesis [88, 89] or immunoabsorption of serum with a staphylococcal protein A column [90, 91] often reverses the kidney injury. Intractible cases have also been treated successfully with rituximab [92, 93].

Nephrotoxicity Associated with Antimetabolites Antimetabolites, including purine analogs, pyrimidine analogs, and antifolate agents are commonly used chemotherapy agents. Nephrotoxicity is induced frequently by methotrexate (an antifolate agent), the best described toxicity associated with any of the antimetabolites. In one series, renal toxicity was reported in nearly 2 % of patient with osteosarcoma who were treated with high-dose methotrexate [94]. Methotrexate doses less that 0.5–1 g/m^2 is often not associated with nephrotoxicity, baring preexisting renal failure. The pathogenesis of methotrexate induced kidney injury is multifactorial. At high dose, methotrexate and its metabolite, 7-hydroxymethotrexate can precipitate in renal tubules, resulting in tubular obstruction. The risk of such intratubular precipitation is heightened by acidic urine, and a volume depleted state. Urine alkalinization and volume expansion lower the risk of precipitation and are often employed as preventative measures. Drugs, including salicylates, probenecids, sulfisoxazole, penicillins, and NSAIDS competitively inhibit tubular secretion of methotrexate, thereby increasing the risk of tubular injury [95]. Methotrexate can also produce a transient decrease in GFR due to afferent arteriole constriction [96], which reverses upon cessation of the drug.

Risk Factors for Chemotherapy-Induced Nephrotoxicity Patient risk factors for chemotherapy-induced nephrotoxicity include: older age, underlying AKI or CKD, pharmacogenetics favoring drug toxicity. Volume depletion can enhance innate drug toxicity due to increased drug or metabolite concentration in the kidney and may involve formation of intratubular crystals by insoluble drug or metabolites. Renal hypoperfusion can be due to decreased oral intake, over diuresis, chemotherapy-induced cardiomyopathy, malignant ascites, or pleural effusion [97]. Tumor-related factors predisposing to chemotherapy-induced nephrotoxicity include the presence of toxic tumor proteins such as with myeloma-related kidney injury, renal infiltration by lymphoma, and cancer-associated glomerulopathies.

Postrenal Causes

AKI associated with postrenal causes is often due to obstruction of urinary outflow secondary to calculus formation, metastatic abdominal/pelvic malignancy,

hemorrhagic cystitis, neurogenic bladder, retroperitoneal lymphadenopathy or fibrosis. Once suspected, the diagnosis is often confirmed by imaging (ultrasound or computed tomography) with demonstration of bilateral hydronephrosis, or unilateral hydronephrosis in patients with single kidneys. In the setting of hypovolemia, acute/partial obstruction, and some cases of retroperitoneal fibrosis, imaging may be falsely negative. Diagnostic utility of biomarkers have been reported [98], but clinical applicability is yet to be established. Timely relief of the obstruction often reverses the AKI. Relative to prerenal and intrinsic renal, postrenal AKI is associated with a higher recovery rate [99].

The Cost and Adverse Outcomes of AKI in Cancer Patients

Increased Mortality

The consequences of AKI in cancer patients are both immediate and long term in onset. Mortality is the most important consequence. A recent, RIFLE-based study from MD Anderson Cancer Center specifically examined the acute costs and outcomes of incident AKI in critically ill patients with cancer. Lahoti and coworkers reported that, among the 2398 ICU cancer patients enrolled in the study, patients who developed AKI during the course of their care had higher mortality relative to those who did not [4]. This is not unlike the known association of AKI and increased mortality among noncancer patients where AKI-related mortality rates are generally reported to be between 30 and 60 % [100]. What was most notable in the study was the close correlation between risk of mortality and the percent increase in serum creatinine from baseline, irrespective of cancer type. Cancer patients with ≥ 50 % change in serum creatinine concentration (risk), ≥ 100 % (injury), or ≥ 200 % or requiring dialysis (failure) had 60 day survival of 62, 45, and 14 %, respectively. A 10 % rise in creatinine increased the odds of 60-day mortality by 8 % [4]. Thus, the more severe the reduction in eGFR, the worse the outcome. The high mortality associated with AKI in cancer patients was supported by other studies [5, 101, 102].

Higher Rate of Failure to Achieve Complete Remission

The incidence of AKI is associated with failure of cancer survivors to achieve complete remission of their cancer. Canet and coworkers recently reported that, among patients with high grade hematological malignancies who did not have preexisting CKD, complete remission rate at 6 months was 39 % compared to 68 % among cancer patients without AKI [5]. Similar to the relationship between mortality and RIFLE classification of AKI, the likelihood of complete remission declines according to percentage rise in creatinine, irrespective of the cause of the AKI. The only exception to this relationship is tumor lysis syndrome. The 6 month complete remission rate in

patients with AKI due to TLS was similar to those of patients without AKI [5]. TLS is a marker of good tumor response to chemotherapy. Therefore, it is logical that when TLS is diagnosed, and treated early, the AKI will not prevent a better outcome due to more effective cancer therapy.

The link between AKI and incomplete cancer remission may be explained by an associated administration of suboptimal dose of chemotherapy—due to chemotherapy dose adjustment necessitated by declining GFR. The higher mortality of cancer patients with AKI may also have an independent contributory effect. Additional mechanisms, however, are also likely involved. When full dose chemotherapy was administered to patients with hematologic malignancies complicated by AKI [5], the incidence of complete remission was still lower. The mechanism underlying this observation is not known. It is also possible that altered pharmacokinetics of chemotherapy in a patient with AKI may alter the response of the cancer to the agent.

AKI Increases the Cost of Hospitalization

The degree of increase in serum creatinine correlates with an increase in cost of hospitalization of cancer patients with AKI. Lahoti et al. showed that, compared to cancer patients without AKI, hospital cost increased by 0.16 % per 1 % increase in creatinine for cancer patients with incident AKI. Hospital costs increased by 21 % for cancer patients with AKI requiring dialysis [4].

Increased Risk of CKD

There is a reciprocal relationship between AKI and CKD. Patients with CKD are at higher risk of developing AKI; but AKI also increases the risk of incident CKD as well as accelerates the progression of preexisting CKD [34, 35]. A recent meta-analysis of 13 studies shows that, compared to patients without AKI, patients with AKI had higher risk of developing CKD and ESKD with pooled adjusted hazard ratios of 8.8 and 3.1 [103]. Among long-term survivors of hematopoietic stem cell transplant, AKI was associated with an increased risk of CKD (HR 1.7) [104]. A recent retrospective, longitudinal study of patients who survived more than 10 years after myoablative allogeneic HSCT showed a cumulative increased incidence of CKD which reached 34 % at 10 years. Acute kidney injury is a strong risk factor for development of CKD. Patients who did not have AKI did not develop CKD [105]. Also, the adjusted hazard ratio appeared to increase with the severity of AKI (based on AKIN classification). Patients are more likely to develop CKD in the first year following HSCT (15 %) than in any subsequent years [105]. The precise mechanism by which AKI accelerates CKD in humans is an area of ongoing active research with our understanding of the genesis of interstitial fibrosis as a central focus of study [106, 107]. Inhibition of this

maladaptive fibrotic process is a focus of research focused on interrupting the link between AKI and CKD as well as CKD progression [108].

Recognizing that CKD is the most important risk factor for cardiovascular disease, progression to ESKD, infection, hospitalization and death [109–111], it is clear that preventing the development of CKD, by preventing AKI among cancer patients, is an important goal for nephrologists and oncologists.

Summary

This chapter highlights AKI as a common event among patients with cancer. Renal toxicity of chemotherapy agents, direct and indirect renal complication of malignancies themselves, as well as advancing age of patients with cancer all converge to increase the risk of kidney disease. Important prerenal, intrinsic renal, and postrenal etiologies have been discussed. The cost and long-term implications of AKI in the context of cancer management are also discussed. Effective management of patients with cancer depends not only on the judicious use of ever emerging, potent chemotherapeutic agents, but also on learning how to better prevent and manage AKI, which often complicates such care. Future research should be aimed at developing noninvasive, sensitive, and specific biomarkers that could expedite early/timely diagnosis. Some patients with cancer seem more vulnerable to nephrotoxins than others. Therefore, research aimed at uncovering patient-specific vulnerability factors will be essential as we enter the age of personalized medicine. Lastly, we do not yet understand the mechanism by which AKI accelerates CKD progression. Progress in this area of research will significantly reduce the short and long-term consequences associated with AKI.

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Chapter 2
Chronic Kidney Disease (CKD) in Cancer Patients

Mala Sachdeva, Amit Lahoti and Anna Mathew

List of Abbreviations

ACE	Angiotensin converting enzyme
AKI	Acute kidney injury
ARB	Angiotensin II receptor blocker
CKD	Chronic kidney disease
CIN	Contrast induced nephropathy
ESA	Erythropoietin stimulating agent
ESKD	End-stage kidney disease
FGF	Fibroblast growth factor
GFR	Glomerular filtration rate
HSCT	Hematopoetic stem cell transplantation
NG	Naso-gastric
NJ	Naso-jejunal
PEG	Percutaneous endoscopic gastrostomy
PTH	Parathyroid hormone
VEGF	Vascular endothelial growth factor

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Table 2.1 Stages of chronic kidney disease (Adapted from the National Kidney Foundation, Kidney Disease Outcome Quality Initiative (K/DOQI). Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kid Dis. 2003;42:S1–201)

Stage	GFR (mL/min/1.73m^2)	Description
1	90+	Normal kidney function but urine or structural abnormalities
2	60–89	Mildly reduced kidney function
3a	45–59	Moderately reduced kidney function
3b	30–44	
4	15–29	Severely reduced kidney function
5	< 15 or on dialysis	Very severe or end-stage kidney failure

Chronic kidney disease (CKD) is defined by a slow and persistent decrease in glomerular filtration rate (GFR) often associated with structural abnormalities of the kidney. Depending on whether there are structural abnormalities or functional decline of kidney function, CKD is classified into different stages (see Table 2.1). CKD is defined as having decreased renal function or structural abnormality for at least a duration of 3 months [1, 2]. The kidney damage is assessed by abnormalities in urinary sediment such as albuminuria or renal imaging, whereas kidney function is assessed by GFR.

In the USA, the prevalence of CKD and end-stage kidney disease (ESKD) is increasing [3]. Studies have shown that older age, diabetes, hypertension, cardiovascular disease, and higher body mass index are associated with CKD [3–5]. The increase in prevalence of CKD is partly explained by the increase in a number of these CKD risk factors.

CKD and cancer are connected in several ways. Not only can cancer—often indirectly, as discussed below—lead to the development of CKD and ESKD but also presence of CKD can be associated with cancer.

Although the overall incidence and prevalence of CKD among cancer patients is still uncertain, there is growing evidence to suggest that the risk is high and still increasing. The extent of risk for developing CKD varies depending on whether the cancer is solid or hematologic in nature, whether patient underwent nephrectomy or hematopoetic stem cell transplantation (HSCT), or whether nephrotoxic chemotherapy was administered.

Case #1

Which of the following patients have an increased risk of developing CKD:

a. A 45-year-old female who is being treated for colon cancer
b. A 75-year-old woman with recent diagnosis of multiple myeloma with cast nephropathy

c. A 50-year-old male who just underwent hematopoeitic cell transplantation for non-Hodgkin's lymphoma
d. All of the above

Solid Malignancies and CKD

In a study of 4864 adult, solid cancer patients having the five most frequently occurring types of cancer (breast, colorectal, lung, ovarian, and prostate), it was reported that 57.4 and 52.9 % of patients had an abnormal creatinine clearance of less than 90 mL/min when calculated with the Cockcroft–Gault formula and the modification of diet in renal disease (MDRD) formula, respectively [6]. Similarly, in a more recent study of 1218 adult, solid cancer patients receiving chemotherapy, 64.0 % were found to have a decreased GFR of less than 90 mL/min/1.73 m^2. Since different cancer types behave differently and their treatments are different, all cancer patients, regardless of the type of cancer, were found to have increased risk of renal insufficiency [7]. Both studies suggest that the frequency of renal insufficiency is routinely underestimated when the physician bases their judgment on the serum creatinine alone. Thus, renal function must be estimated with formulas which take into account gender, age, and weight of an individual [6, 7]. In addition, both studies excluded those with multiple myeloma and hematologic malignancies. Had these populations been included, the burden of CKD would evidently have been higher.

Multiple Myeloma and CKD

In patients with multiple myeloma, impaired renal function is present in more than 20–30 % of the population at the time of diagnosis [8, 9]. At some point in their disease course, approximately 50 % of them may develop acute kidney injury (AKI) or CKD [9]. Renal failure was more prevalent in those who had more severe hypercalcemia, anemia, and Bence Jones proteinuria [9]. Reversibility of renal failure depended on serum creatinine levels, presence of hypercalcemia, and the extent of proteinuria [8]. Survival was significantly less in those who had renal failure as compared to those with normal renal function, with median survival ranging from 4 months to 1 year, as shown in another study [8].

HSCT and CKD

HSCT is performed more frequently for various hematologic malignancies. CKD following HSCT has been shown to be relatively common and occurring in approximately 16.6–23 % of HSCT patients [10–12]. Some literature suggests higher rates

depending on definition of CKD. Risk factors for CKD in this population included: AKI, total body irradiation, graft versus host disease, and long-term calcineurin inhibitor use [10].

Case #1 Follow Up and Discussion
The correct answer is choice d. As discussed above, solid malignancies, multiple myeloma, and HSCT have all been associated with development of CKD.

CKD and Cancer Development

Case #2
A 71-year-old female is on hemodialysis for the past 4 years. Which of the following cancer is she at most increased risk of developing?
a. Lung cancer
b. Breast cancer
c. Kidney cancer
d. Colon cancer

Studies over the past 30 years have suggested an increased risk of developing cancer in patients with ESKD. Population based studies have also shown an association of mild to moderate CKD and an increased risk of cancer. Potential reasons for this increased risk include the presence of chronic urinary tract infections, a weakened immune system, prior treatment with cytotoxic or immunosuppressant drugs, nutritional deficiencies, and impaired DNA repair mechanisms. Other risks include the environmental exposures leading to cancer and renal failure or acquired cystic renal disease [13, 14].

Cancer rates are higher in patients with ESKD on hemodialysis compared to the general population. In a retrospective analysis of over 800,000 patients on dialysis over an average follow up of 2.5 years, the standardized incidence ratio of cancer was 1.18. Kidney, bladder, thyroid, and Kaposi's sarcoma had the highest risks. Patients on dialysis have increased risk of lower urinary tract disease and are more susceptible to viral carcinogenesis (e.g., hepatitis B and C). The risk of kidney cancer increases with increased time on dialysis. This seems to be secondary to acquired cystic renal disease associated carcinoma. Other risk factors for cancer include dialysis-induced immune dysfunction, prolonged analgesic abuse, and carcinogenesis from prior immunosuppressive or cytotoxic therapy. ESKD after stem cell transplant is associated with increased mortality compared to ESKD from other causes. The cancer risk after

starting dialysis has been shown to increase from 10 to 80 %. [15, 16]. Of a cohort of 831,804 patients on dialysis in the USA, Europe, Australia, and New Zealand, 3 % developed cancer after 2.5 years of follow up [14]. There was a higher risk of cancer in patients younger than 35 [14]. In addition, there was a high risk of kidney, bladder, thyroid, and other endocrine organs [14]. Activation and exposure to viruses such as hepatitis B and C, Epstein–Barr virus, and human papillomavirus likely accounted for the increased risk of other types of cancer. Contrary to bladder cancer, the risk of kidney cancer increased with time on dialysis. Acquired renal cystic disease on dialysis may contribute to this risk. There was difference in risk for cancer between hemodialysis and peritoneal dialysis. Higher rate of cancer was detected in Australia and New Zealand versus Europe and the USA. However, this may be the result of ascertainment bias given the under reporting of cancer in the latter. In another analysis from three large dialysis registries in the USA, Europe, and Australia, cancers of the kidney and bladder were more common, and there was increased risk relatively in the younger population and the female patients [13]. In a study of 28,855 patients who were on dialysis, there was a fourfold increase in ESKD related cancers, namely kidney, urinary tract, and thyroid cancers and a smaller yet still increased risk of cancers, 20 related to immune deficiency [16]. For all cancers, the risk was higher in the individuals less than 50 years old [16].

Studies on the CKD population have been conducted to determine the association of CKD and cancer risk in the older population. One such study from Australia demonstrated that men with CKD had an increased risk for cancer. This risk for men began at an eGFR of 55 ml/min/1.73 m^2, and posed a greatest risk when eGFR was less than 40 ml/min/1.73 m^2. Men with CKD were more at risk for lung and urinary tract cancers [17]. In a more recent analysis, eGFR < 60 mL/min/1.73 m^2 appears to be a significant risk factor for death from cancer [18]. The excess cancer mortality in those with reduced kidney function varied with site, with the greatest risk in those with breast and urinary tract cancer [18]. Each decrease in eGFR by 10 ml/min/1.73 m^2 increased the risk of cancer by 29 % in men. Lung and urinary tract cancers comprised most of the excess cancer risk. Residual confounding (e.g., occupational exposures) was speculated to explain the lack of increased cancer risk in women with CKD. [18]

CKD is also a significant risk factor for both cardiovascular and non-cardiovascular mortality in patients with cancer. Fried et al. were one of the first to show an increase in cancer mortality in patients with decreased renal function [19]. Among 4637 patients in the Cardiovascular Health Study, patients with cystatin C levels in the fourth quartile versus the first quartile had a 79 % increase in cancer mortality rate. The IRMA study was a French observational study that included 4684 patients with cancer, of which 53 % had a eGFR less than 90 ml/min/1.73 m^2 and 12 % had an eGFR less than 60 ml/min/1.73 m^2 [20]. Patients with CKD stage 3 or lower had a 27 % higher mortality. Over one half of these patients required a dose adjustment of chemotherapy, reflecting a practical impact of CKD on this population. In another study of 8223 patients in Korea, CKD was an independent predictor of cancer-specific mortality, which remained significant in a multivariate model [21]. Iff et al. studied 4077 patients in the Blue Moutains Eye Study and found an 18 % increase in mortality for every 10 ml/min/1.73 m^2 reduction in eGFR [18]. Breast

and urinary tract cancers conferred the greatest risk of mortality among patients with CKD. The largest study to date included a cohort of 123,717 patients with a median follow up of 7 years [22]. Patients with CKD had a 20 % increase in cancer mortality compared to patients with normal renal function. Baseline CKD was associated with an increased risk of hepatic, renal, and urinary tract malignancies. Poor nutrition, increased oxidative stress, proinflammatory state, and procoagulant state were proposed as mechanisms for the increased cancer risk in these patients.

Proteinuria is also associated with the development of cancer. In a 10 year follow up of 5425 patients without diabetes or macroalbuminuria, each standard deviation of albuminuria (log of albumin to creatinine ratio) was associated with a 20 % increased risk cancer [23]. Patients with the highest quintile of albumin-to-creatinine ratio compared to the lowest quintile had a relative risk of 8.3 and 2.4 for the development of bladder and lung cancer, respectively.

Case # 2 Follow Up and Discussion
The correct answer is choice c. While dialysis patients are at increased risk for all malignancy, the highest risk is cancer of the urinary tract. Kidney and bladder malignancies are the most common.

Screening for CKD in Cancer Patients

Case #3
A 70-year-old Caucasian female with a history of membranous nephropathy diagnosed 3 years ago was diagnosed with colon cancer shortly thereafter. She was treated with surgical resection and adjuvant oxaliplatin-based chemotherapy for colon cancer and is now in remission. On routine laboratory tests she is found to have a serum creatinine of 1.5 mg/dL. She is 160 cm tall and weighs 65 kg. Urine studies from 3 years ago revealed 5 g of proteinuria and laboratory studies at that time revealed a creatinine of 1.0 mg/dL. One year ago her creatinine was 1.2 mg/dL. At that time, her urinalysis was not significant for proteinuria or microscopic hematuria. Which of the following is correct?

a. The patient has AKI
b. The patient has CKD stage 1
c. The patient has CKD stage 2
d. The patient has CKD stage 3
e. The patient has CKD stage 4

In the general population, there is some controversy as to whether routine screening for CKD by blood work and/or urine testing is cost-effective. However, it should be a priority to define and grade CKD in cancer patients, by checking a serum creatinine

Table 2.2 GFR estimating equations

Cockcroft Gault (in mL/min)	$\frac{(140-\text{age})\times\text{weight}}{72\times\text{SCr}} \times (0.85 \text{ if female})$
MDRD (in mL/min/1.73 m^2)	$185 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$
Jelliffe (in mL/min)	$\{[98 - 0.8 \times (\text{age}-20)] \times [1 - (0.01 \times \text{sex})] \times (\text{BSA}/1.73)\}/(\text{SCr} \times 0.0113);$
Wright (in mL/min)	$\{[6580 - (38.8 \times \text{age})] \times \text{BSA} \times [1 - (0.168 \times \text{sex})]\}/\text{SCr}$

SCr Serum Creatinine in mg/dL
Sex: Male = 0; Female = 1
BSA Body surface area (DuBois)
Age: in years
Weight: in kilograms

and estimating GFR. Since kidney plays a pivotal role in drug elimination, having a good estimate of kidney function is essential for proper drug dosing especially that of many chemotherapeutic agents.

Case #3 Follow Up and Discussion
The correct answer is choice d. For the patient in this question, it is likely that she has CKD given that her creatinine has been elevated for more than a 3 month period. Her history of membranous nephropathy could be a potential contributing factor. While cisplatin has been associated with tubular toxicity, there have been no reports of oxaliplatin-induced nephrotoxicity [24]. After estimating her GFR, she is found to be at stage 3 CKD with an estimated creatinine clearance of 35 mL/min using the Cockcroft–Gault equation.

In addition, as stated earlier, CKD is an independent risk factor for cardiovascular disease, progression to ESKD, and all cause mortality [25–28]. This in itself can be helpful at preventative behaviors.

GFR can be measured directly by measuring renal excretion of radioisotopes or by nuclear renogram. Whereas these measures are highly accurate and directly measure GFR, they are expensive and not often readily available. A more common method to ascertain kidney function is by estimating the GFR through one of several available estimating equations. These equations use readily available variables such as serum creatinine, age, gender, weight, and race and are listed in Table 2.2.

The Cockcroft–Gault is the most commonly used equation and the modified Jelliffe formula is used in several oncology trials for the purpose of estimating GFR. Recently, the MDRD equation has gained popularity, but was derived in a healthy population, and is currently not recommended for use in the oncology patient. Based on recent literature comparing various GFR-estimating equations in oncology patients, it is currently recommended to use the Cockcroft–Gault equation [29]. If the GFR is greater than equal to 50 ml/min and the patient is greater than 70 years and/or

BMI greater than equal to 30, the Wright formula gives the best estimate of GFR [24] (See Table 2.2).

Microalbuminuria is defined at 30–300 mg/day of urine albumin and thus is not detected by a urine dipstick test alone. Urine protein is comprised of albumin and Tamm—Horsfall proteins. In certain hematological malignancies, light chains are also excreted in the urine, called Bence Jones proteins. This abnormal proteinuria is not detected by urine dipstick test.

Checking urine for microalbumin is a simple and important tool to detect individuals with early or undiagnosed CKD. When microalbuminuria is present, GFR is typically elevated, normal, or slightly impaired [30]. Microalbuminuria is defined as 30–300 mg/day of urine albumin, and macroalbuminuria is defined as greater than 300 mg/day of urine albumin. Following are the ways to check for microalbuminuria/proteinuria: (1) urine albumin-to-creatinine ratio (ACR), (2) urine protein-to-creatinine ratio (PCR), (3) reagent strip urinalysis for total protein with automated reading, and (4) reagent strip urinalysis for total protein with manual reading. In all of the above, an early morning urine sample is preferred, and the test should always be confirmed [2].

Albuminuria is not only important for detecting CKD, but its significance in long-term prognosis bears relevance. It is associated with increased all-cause and cardiovascular mortality, as well as progression to end-stage renal disease. These risks exist even in the absence of a reduced GFR [31].

Management of the Cancer Patient with CKD

Drug Dosing and Polypharmacy

Abnormal renal function serves as a risk factor for drug induced nephrotoxicity. In patients with CKD, drug pharmacokinetics may be altered. For example, some drugs that are dependent on protein binding may end up in higher than normal concentrations due to hypoalbuminemic states. Other drugs may have altered renal excretion due to the reduction in GFR [20]. Approximately half of all anticancer drugs are excreted in the urine as active metabolite or unchanged drug. Due to decreased clearance issues, these drugs need adjustment to avoid accumulation of toxic metabolites or overdosage of the medication [6]. In the CKD population, choosing the non-nephrotoxic or less nephrotoxic drug would be ideal. However, in cancer patients requiring chemotherapy, the therapeutic options are often limited. For this reason, drug-induced nephrotoxicity should be noted, discussed, and appropriately monitored and managed according to the medication guidelines.

Another important factor is drug–drug interactions. A careful review of medications is important to avoid the risk of combining anticancer and non-anticancer medications interactions [7]. For example, NSAIDs and ACE inhibitors may potentiate nephrotoxicity especially in a volume-depleted individual.

Finally, the potential of further deterioration of renal function with chemotherapy, which would then precipitate ESKD, must be considered [6]. In this situation, timely referral to a nephrologist would be ideal to allow for timely discussions with the patient regarding options of either renal replacement therapy or end of life issues.

Hypertension

Case #4
You are seeing a 55-year-old white female with a creatinine of 1.5 mg/dL in your office. She has recently been diagnosed with breast cancer and is awaiting assessment by surgical oncology. She is a current smoker. Her blood pressure has been 160/95 and 155/90 mmHg when checked last 2 times in your office. Her albumin to creatinine ratio in the urine is 50 mg/g, and her serum potassium is 5.2 mEq/L. What is the best initial intervention?

a. Life style interventions including daily exercise, DASH diet, and smoking cessation
b. Initiation of an angiotensin converting enzyme (ACE) inhibitor
c. Initiation of an ACE inhibitor and a thiazide-type diuretic
d. a and b
e. a and c

Hypertension is one of the most common comorbidities encountered with malignancy. Preexisting hypertension, as well as hypertension due to certain chemotherapy agents, account for the majority of those with hypertension [32–34] (See Table 2.3). In addition to these medications, surgery or radiation therapy involving the head and neck can be associated with hypertension. The mechanism of this is thought to be baroreflex failure, causing either labile hypertension or hypertensive crisis. Managing hypertension is important in this patient population to reduce long-term adverse consequences and decrease progression of CKD [32].

Case #4 Follow Up and Discussion
The correct answer is choice e. Life style interventions and initiation of an ACE inhibitor and thiazide-type diuretic. According to the most recent JNC VIII guidelines for hypertension management [32], patients with CKD of all ages and all races should have a goal blood pressure of less than 140/90 mmHg. Lifestyle interventions should be implemented throughout the course of treatment. While initial choice of medication should be individualized, an ACE inhibitor or an angiotensin receptor blocker (ARB) should be considered as first line of therapy, especially in the case of microalbuminuria. In this case,

Table 2.3 Chemotherapy-induced hypertension

Medication	Class	Reason for hypertension
Tamoxifen	Estrogen receptor binder	Via estrogenic effects
Cyclosporine	Calcineurin inhibitor	Endothelial dysfunction, arterial vasoconstriction and activation of the renin–angiotensin system
Cisplatin	Alkalating agents	Possible drug induced renovascular mechanisms
Dexamethasone, prednisone	Steroids	Salt and fluid retention
Bevacizumab	Vascular endothelial growth factor (VEGF) monoclonal antibody	Inhibition of VEGF signaling pathway leading to suppression of nitric oxide synthase, resulting in decreased nitric oxide production and reduced prostacyclin activity in the endothelium
Sorafenib, sunitinib, pazopanib, vandetanib, axitinib, regorafenib, cabozantinib	Small molecule tyrosine kinase inhibitor	Inhibition of VEGF signaling, as above
Aflibercept	Recombinant fusion protein which prevent VEGF receptor binding/activation to their receptors	Inhibition of VEGF signaling, as above

a thiazide-type diuretic should also be employed to help control both blood pressure and serum potassium. In the African American population, the first line treatment may be a calcium channel blocker or thiazide-type diuretic.

Initial approach to hypertension would be lifestyle modifications such as weight loss, increased physical activity, DASH diet, and moderate alcohol consumption. Pharmacologic therapy should be instituted if blood pressure remains high.

According to the most recent JNC VIII guidelines, goal blood pressure for those who are 60 years or older should be less than 150/90 mmHg. A target blood pressure of less than 140/90 mmHg is recommended in all other age groups and in hypertensive patients with diabetic or non-diabetic CKD [32]. The choice of which antihypertensive agent should be used depends on the patient's comorbidities and ethnicity. In the nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, ACE inhibitor, or ARB. In the black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker. Patients with CKD and hypertension should be started on ACE inhibitor or ARB.

Metabolic Bone Disease

Case #5
A patient recently diagnosed with squamous cell carcinoma of the lung has underlying CKD stage 4 (eGFR when last checked was 25 mL/min/1.73 m^2) related to preexisting hypertension. A recent staging computed tomography (CT) scan found no distant metastases, but local spread to bilateral lung fields. She is found unconscious, brought to hospital, and the serum calcium is 12 mg/dL. Which of the following laboratory values are most likely consistent with the patient's presentation?

a. Serum iPTH < 12 pg/mL (low), 1,25-vitamin D > 60 pg/mL (high), 25-vitamin D < 30 pg/mL (low)
b. Serum iPTH 35 pg/mL, 1,25-vitamin D < 20 pg/mL (low), 25-vitamin D < 30 pg/mL (low)
c. Serum iPTH < 12 pg/mL, 1,25-vitamin D < 20 pg/mL, 25-vitamin D < 30 pg/mL (low)
d. None of the above

Mineral and bone disorders in patients with CKD are a result of dysfunction in the complex interdependence of phosphorus, vitamin D, calcium, and parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF 23). Early-stage kidney disease results in phosphate retention from decrease in filtration.

Case #5 Follow Up and Discussion
The correct answer is choice c. This patient most likely has humoral hypercalcemia of malignancy, which is due to PTH-related peptide secretion by the tumor. In this setting, endogenous PTH secretion and production of vitamin D are suppressed. While humoral hypercalcemia of malignancy is typical of squamous cell carcinomas and cancers of the kidney, bladder, breast, and ovaries, it can be seen in any non-metastatic solid organ tumor. Hodgkin and non-Hodgkin's lymphoma is associated with increased production of 1,25 vitamin D as the main mechanism contributing to hypercalcemia.

Phosphaturia is initially promoted through an increase in FGF 23 and appropriate hypersecretion of PTH. Serum phosphate levels begin to rise at an eGFR of less than 30 mL/min/1.73 m^2 [35]. Decreased formation or activity of 1,25-dihydroxyvitamin D (normally produced by the kidney) leads to hypocalcemia, an additional stimulus for PTH secretion. Initial management hinges on low dietary intake of phosphate, with sequential introduction of phosphate binders and activated vitamin D. Secondary hyperparathyroidism eventually occurs due to a variety of mechanisms [36]

contributing to bone diseases. Calcimimetics, which bind to the calcium-sensing receptor, are used to reduce PTH secretion, and occasionally parathyroidectomy is required for tertiary hyperparathyroidism.

Renal osteodystrophy refers to a variety of bone pathologies seen in patients with CKD. These have been identified as: (1) high bone turnover due to secondary hyperparathyroidism (Osteitis fibrosa cystica), (2) low bone turnover due to excessive PTH suppression (adynamic bone disease), (3) low bone turnover in combination with abnormal bone mineralization (osteomalacia), (4) a combination of turnover and mineralization abnormalities (mixed uremic osteodystrophy), or (5) beta 2 microglobulin associated amyloid bony deposits [37].

The new field of literature in "Osteoncology" speaks to the many clinical considerations required in patients with bone involvement of their malignancy. These include bony metastases, hypercalcemia of malignancy, bone toxicity of chemotherapeutics, and the use of bisphosphonates and the newer anti-RANKL antibodies, such as denusomab. Just as in the uremic patient, cancer cells produce a microenvironment in bone which disrupts the normal balance of osteoclasts and osteoblasts, thus forming lytic, blastic, or mixed bony lesions [38]. Bone metastases are the most common malignant manifestation in bone. Carcinomas of prostate, breast, and lung most commonly spread to bone, along with kidney, thyroid, and melanoma. Only 25 % of patients with bony metastases remain asymptomatic, and the remainder undergo a range of clinical presentations including pain, pathological fracture, bone marrow suppression, and spinal cord compression.

For bone disease in certain metastatic cancers and humoral hypercalcemia of malignancy, bisphosphonates have been approved. Bisphosphonates decrease bone resorption and increase mineralization by inhibiting osteoclast activity.

The bisphosphonates used in metastatic cancers are predominantly administered in intravenous forms, such as zoledronate and pamidronate. These bisphosphonates are excreted unchanged through glomerular filtration by the kidneys. In patients with CKD, bisphosphonate excretion is reduced due to decreased renal function. This could result in excessive serum and bone levels, and dose adjustments are required based on estimated GFR. Bisphosphonates should be used at reduced dosages in those with CKD. In addition, longer dose intervals and slower infusion times should be preferred as there is a dose-dependent and infusion time-dependent relationship with the nephrotoxicity [39]. Serial creatinine levels should be monitored. Hydration should be provided especially for those with multiple myeloma and Bence Jones proteinuria. Concurrent usage of nephrotoxic medications should be avoided as well. In those with creatinine levels above 3 mg/dL and creatinine clearance less than 30 mL/min not much is known regarding the pharmacokinetics. For this reason, the use of pamidronate in patients with severe renal impairment is not recommended when treating bone metastasis in this subset of patients. For other indications, clinical judgment should determine whether the potential benefit outweighs the risk in such patients [40].

Both zolendronate and pamidronate are reported to cause nephrotoxicity. Collapsing focal segmental glomerulosclerosis and other glomerular diseases such as minimal change disease are reported with pamidronate [41, 42]. In addition, there are case reports of tubulointerstitial nephritis and acute tubular necrosis with pamidronate [43, 44]. Zolendronate is reported to cause acute tubular necrosis [44, 45].

Denusomab is approved for cancer with bone metastasis. It is a monoclonal antibody targeting receptor activator of nuclear factor kappa B ligand (RANKL) and inhibits osteoclast formation and activation. It is used in the management of patients with breast and prostate cancer who are at risk for bone loss due to cancer treatments (e.g., aromatase inhibitors or androgen deprivation therapy) [46, 47]. Denusomab is not cleared by the kidneys, thus it does not have to be dose-adjusted for renal function. However, patients with severe CKD (eGFR < 30 mL/min/1.73 m^2) are susceptible to hypocalcemia and should be monitored closely for the duration of treatment.

Anemia

Case #6
In patients with concomitant severe CKD (eGFR < 30 mL/min/1.73 m^2) and an active malignancy, symptomatic anemia should be treated initially with:
a. Red blood cell transfusion
b. Erythropoietin stimulating agents (ESAs)
c. Intravenous Iron
d. All of the above

The anemia of CKD is due to the reduction of erythropoietin production by the kidney and shortened red cell survival [48]. Anemia in these patients becomes increasingly common as the GFR falls below 60 mL/min/1.73 m^2 [49], and is characterized by either microcytosis or normocytosis. Routine management of CKD patients includes diagnosis and management of iron deficiency, a common contributing cause to CKD-associated anemia. Treatment with ESAs is part of the chronic management in patients with CKD, and has been studied and utilized extensively in this patient population. Anemia is also a common complication in the cancer patients. Etiology is multifactorial and includes suppression of erythropoietin production by the tumor, myelosuppressive cancer treatment, and underlying blood loss or deficiencies of folate, vitamin B12, or iron. In contrast to CKD patients, ESAs in cancer patients are used most commonly in the setting of anemia associated acutely with myelosuppressive treatment, rather than part of chronic treatment.

Case #6 Follow Up and Discussion
Symptomatic anemia should always be treated with red blood cell transfusion initially, irrespective of renal disease or malignancy. Once stabilized, and other reversible causes of anemia are addressed (gastrointestinal bleeding, iron, vitamin B12, or folate deficiency), then decision to initiate an ESA must carefully weigh the risks of thrombosis and mortality with the benefits of reduced symptoms and need for further transfusions. Anemia in this patient is multifactorial, related to decreased erythropoietin production from CKD, as well as inflammation and myelosuppressive chemotherapy related to the malignancy. If an ESA is initiated in this patient, the upper hemoglobin target should be maintained at 10 g/dL, and close monitoring is required for development of thromboembolic events. The correct answer is choice a.

The risks and benefits and use of ESAs in the CKD and cancer patient populations have been studied extensively. While the hemoglobin response to ESAs has been well-characterized in CKD patients, response tends to be slower and less predictable in cancer-associated anemia [50]. ESAs have been shown to improve quality of life as well as the need for blood transfusions in CKD patients. [51–53]. Several large randomized controlled trials were conducted to determine the optimum target hemoglobin when treating CKD patients with ESAs [54–57]. However, results from these studies have raised concerns over the safety of ESA use when targeting hemoglobin in the normal range, with adverse events including stroke, thrombotic disease, hypertension, adverse cardiac events. In addition, increased thrombotic events or mortality were also reported in patients with CKD and concomitant cancer. It has been hypothesized that malignant cells have erythropoietin receptors, and that administration might therefore accelerate tumor growth [58]. In cancer patients, ESA use has been studied in clinical trials and shown to increase hemoglobin and reduce transfusion requirements [59]. However, as with the treatment of CKD-related anemia, significant concerns have been raised from recent trials, given the finding of inferior survival and increased thrombotic risk in cancer patients treated with ESAs. [60, 61].

Clinical practice guidelines have been published for the management of anemia in CKD and cancer patients. The recent 2012 KDIGO guidelines for CKD patients recommend refraining from ESA initiation in CKD patients until the hemoglobin falls to less than or equal to 10 gm/dL. The guidelines also advise extreme caution in the administration of ESAs to CKD patients with active malignancy, and/or a history of stroke. The American Society of Hematology and American Society of Clinical Oncology have published guidelines on the use of ESA in cancer patients. [62, 63]. It was advised that ESA use should be avoided in cancer patients not undergoing active chemotherapy, other than to avoid repeated transfusions in patients with lower risk myelodysplastic syndromes. ESA use was recommended in patients with chemotherapy-associated anemia when the hemoglobin level has fallen below 10 gm/dL.

While approaching a CKD patient with malignancy, the clinician should determine if the anemia is due to underlying CKD (more likely as the GFR falls further below 60 mL/min/1.73 m^2) or to chemotherapy induced myelosuppression. Investigations for blood loss, iron, vitamin B12, and folate deficiency should be undertaken, and individualized approach is required prior to prescribing an ESA. A discussion with the patient regarding the above mentioned risks and benefits of ESA use is essential. Extreme caution is advised in patients with a history of thrombotic disease or stroke, especially if the aim of chemotherapy is curative. If the decision is made to proceed forth with the use of an ESA, regular monitoring of the hemoglobin is required. Target hemoglobin levels should minimize need for transfusion, rather than attempt to normalize hemoglobin levels. Prolonged treatment may be indicated if the primary reason for treatment is CKD associated anemia. A treatment paradigm for patients with CKD and active malignancy has been proposed in the recent literature [64], which suggests initiation of an ESA with upper hemoglobin target of 10 g/dL. In contrast, a short course of ESA is advised in patients with myelosuppression related to chemotherapy.

Radiographic Imaging and Precautions

Case #7
A 45-year-old woman with diabetic nephropathy and a creatinine of 2.2 mg/dL is hospitalized for shortness of breath, and is diagnosed with lung cancer. Her oncologist would like to perform a whole body CT scan with intravenous contrast. He consults you for clearance. Aside from having a detailed discussion with the patient regarding the risks and benefits of this procedure, you also recommend the following:

a. ACE inhibitor for renal protection
b. Normal saline
c. Dialysis

In cancer patients with advanced CKD, radiologic imaging at more than one time during the course of their disease is likely required. More specifically, there may be a need for CT scans with radiocontrast or magnetic resonance imaging with gadolinium.

Case #7 Follow Up and Discussion
Contrast induced nephropathy (CIN) is of concern in someone with CKD. Being elderly, having diabetes, and an elevated creatinine serve as the more common risk factors for development of CIN. Volume repletion is important in preventing CIN. For this patient, hydrating with normal saline would be the best choice. There is no evidence that dialysis can prevent CIN. The correct answer is b.

It is important to take into consideration that if radiocontrast is necessary in an individual with decreased kidney function, then preventative measures including volume expansion with intravenous saline should be administered to prevent CIN [65]. The administration of gadolinium has been linked to nephrogenic systemic fibrosis, a severe and debilitating disease. Due to this, in patients with an eGFR less than 30 mL/min/1.73 m^2 and in patients who are on dialysis, the administration of gadolinium should be avoided [66]. There is no consensus on safety data regarding administering gadolinium in those with eGFR between 30 and 60 mL/min/1.73 m^2. If the decision to perform this imaging is made, risk and benefit discussions with the patients should be undertaken. If a patient on dialysis is to receive gadolinium, then hemodialysis subsequent serial sessions is recommended [67].

Nutrition

While all patients with malignancy are at risk for malnutrition, degree of weight loss and tumor that have malignant tumors have a high prevalence of malnutrition. In a recent study of 3047 patients with 11 different tumor types, patients with favorable subtypes of non-Hodgkin's lymphomas, breast cancer, acute non-lymphocytic leukemia, and sarcomas had the lowest risk of weight loss (31–41 %). Unfavorable non-Hodgkin's lymphoma, prostate cancer, colon cancer, and lung cancer had an intermediate risk of weight loss (48–61 %). Pancreatic and gastric cancer patients had the highest risk of weight loss (83–87 %) [68].

Malnutrition is defined as an imbalance of energy, protein, and other nutrients, measured through adverse effects on patient outcomes, as well as tissue and body composition [69]. Malnutrition is a common complication in advanced CKD (stage 4 and 5) and cancer patients. Lack of appetite as well as inflammation and catabolism play a role in the development of malnutrition in these patients. Depending on the malignancy, additional factors could include mechanical obstruction of the digestive tract (head and neck, esophageal, mediastinal masses, and bowel cancer), early satiety (gastric cancer), or diarrhea (pancreatic or biliary cancer). Chemotherapy and radiation therapy can cause a variety of conditions leading to anorexia such as mucositis, diarrhea, nausea, and changes to smell and taste.

CKD with an eGFR of less than 30 mL/min/1.73 m^2 is independently associated with malnutrition [70]. The term "kidney disease wasting" has been developed to describe the loss of body protein mass in renal disease [71]. This protein-energy wasting can be diagnosed if the following characteristics are present: (1) low serum albumin, pre-albumin, or cholesterol; (2) reduced body mass; and (3) reduced muscle mass (measured by reduced mid-arm muscle circumference). In patients with malignancy, weight loss is independently associated with mortality, as well as a decreased response to chemotherapy [68]. Even an unintentional weight loss of 5 % total body mass can be a significant finding, and should prompt screening for malnutrition. The malnutrition screening tool is a simple three step tool which has been validated for use in outpatients with cancer, to assess the need to refer to a clinical dietician [72].

Once diagnosed with malnutrition, body weight, serum albumin, pre-albumin, and cholesterol concentrations can be used to monitor the patient's nutritional status [73]. Serial measurements are important, as albumin is also a negative acute phase reactant, and low levels can indicate acute inflammation in addition to malnutrition. If left untreated, malnutrition will progress to cachexia, an irreversible syndrome of severe fat and muscle loss with increased protein catabolism. Thus, patients with or at risk of malnutrition should be promptly referred for assessment and receive the appropriate form of nutritional support. Enteral nutrition is preferred either via oral intake or enteric tube (naso-gastric, NG; naso-jejunal, NJ; or percutaneous endoscopic gastrostomy, PEG). If the malignancy involves the gastrointestinal tract, the parenteral nutrition should be considered. At minimum, caloric intake of 30–35 kcal/kg/day is required for adequate nutrition in patients with CKD. High protein intake can induce hyperfiltration through a variety of mechanisms and hasten the progress of CKD. Thus, protein restriction to approximately 0.8 g/kg has been suggested in patients with CKD and eGFR less than 60 mL/min/1.73 m^2. Patients on a protein-restricted diet should follow up closely with a nutrition specialist to monitor for evidence of protein malnutrition and adequate caloric intake.

In addition to nutritional supplementation, progestin-based appetite stimulants such as megestrol acetate and medroxyprogesterone acetate have been used. While these medications have been studied widely in patients with cancer [74], they have substantial renal excretion have not been well-studied in patients with kidney disease. However, one study of ten hypoalbuminemic dialysis patients with malnutrition used half the usual dose (400 mg/day) of megestrol acetate and reported no major side effects with improvement in body fat and serum albumin after 4 months [75]. Corticosteroids are used, usually during palliative cancer care, to stimulate appetite. However, this should be used with care in patients in concomitant renal disease to avoid acute salt and water retention, hypertension, and pulmonary edema.

Renal Replacement Therapy

The decision to initiate chronic renal replacement therapy should be discussed at length between all treating physicians and the patient. This is especially important in the patient with cancer, as the overall goals of care should be congruently presented by the nephrologist and oncologist. Once the decision to initiate renal replacement therapy has been made, the type of dialysis is largely dependent on patient preference. Patient education is crucial to making an informed decision on dialysis modality. Renal transplantation is not an option for patients with active or recent history of malignancy.

Recognizing uremic symptoms in the ESKD patient and preparing the patient for renal replacement therapy in a timely manner is important. Generally, a nephrologist referral should be made as the estimate GFR declines below 30 mL/min/1.73 m^2, so that adequate time is given for placement of vascular access. Clinicians must be vigilant of signs and symptoms of uremia. Indications for starting renal replacement therapy could include: volume overload or persistent uncontrollable hypertension,

refractory metabolic acidosis or hyperkalemia, pericarditis or pleuritis, uremic encephalopathy, severe malnourished state, persistent uremic symptoms such as nausea or vomiting [2]. Other symptoms of uremia could include decreased attentiveness and cognition, depression, pruritis, or restless leg syndrome. Initiating dialysis should be based upon clinical factors and eGFR [2].

It is always important that a clinician involved in the care of the cancer patient with ESKD determine if renal replacement therapy will benefit the particular individual. Conservative management should be an option provided by the health care professional. If the patient decides not to pursue renal replacement therapy, then full support with end of life planning should be offered [2]. ESKD itself is associated with limited life expectancy, high morbidity, and considerable burden of symptoms [76]. If prognosis is poor and quality of life will become even poorer, a palliative approach would be considered reasonable for a particular individual with end-stage cancer. The palliative goal would be to provide relief from symptoms and pain, and to improve the quality of life for both the patient and the family [72, 73]. In certain circumstances when prognosis is short (weeks to months), hospice care can be provided [77]. Physicians and health care professionals should discuss these goals with their patients in advance. An entire chapter in this book has been dedicated to the role of palliative care in patients with cancer and kidney injury.

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Chapter 3
Glomerular Diseases Seen with Solid Tumors and Hematological Malignancies

Hitesh H. Shah

List of Abbreviations

MN	Membranous nephropathy
PLA2R	Podocyte transmembrane glycoprotein M-type phospholipase A2 receptor
KDIGO	Kidney Disease: Improving Global Outcomes
CT	Computed tomography
MCD	Minimal change disease
HIV	Human immunodeficiency virus
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin 2 receptor blocker
PET	Positron emission tomography
FSGS	Focal segmental glomerulosclerosis
HPS	Hemophagocytic syndrome
MPN	Myeloproliferative neoplasms
TMA	Thrombotic microangiopathy
CML	Chronic myelogenous leukemia
PV	Polycythemia vera
ET	Essential thrombocythemia
PMF	Primary myelofibrosis
MPGN	Membranoproliferative glomerulonephritis
CLL	Chronic lymphocytic leukemia
MGUS	Monoclonal gammopathy of undetermined significance
IgAN	Immunoglobulin A nephropathy
HSP	Henoch–Schonlein purpura
CGN	Crescentic glomerulonephritis

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ANCA	Antineutrophil cytoplasmic antibody
FGN	Fibrillary glomerulonephritis
ITG	Immunotactoid glomerulopathy
AAA	AA amyloidosis

Since the association between Hodgkin's disease and albuminuria was described by Galloway in 1922 [1], several types of solid tumors and hematological malignancies have been associated with various glomerular pathology and diseases. The exact pathogenesis of this association remains to be determined. However, it is likely that these paraneoplastic glomerular diseases occur as a result of abnormal products produced by tumor cells and not due to the tumor burden or extent of tumor invasion. The treatment for cancer-associated glomerular diseases is different from the treatment of primary glomerular diseases. Treating the primary cancer has shown to resolve the cancer-associated glomerular process. Therefore, treatment of these paraneoplastic glomerular diseases is directed primarily at treating the underlying cancer. This chapter reviews the glomerular diseases seen with solid tumors and hematological malignancies. Glomerular diseases associated with plasma cell dyscrasias are discussed elsewhere in the book.

Membranous Nephropathy (MN)

Solid Tumor-Associated MN

Case #1
A 70-year-old white male was referred by his primary care physician for evaluation of nephrotic range proteinuria. He was presented with 1 month history of deteriorating bilateral lower extremity edema. He denied past history of diabetes, hypertension, hepatitis, or blood transfusion. Review of systems was significant for unintentional 30-pound weight loss over the past 3 months. He denied fever, chills, dyspnea, gross hematuria, arthralgias, or rash. He also denied use of any medications, including non-steroidal anti-inflammatory drugs (NSAIDs) and herbal medications. There was no history of intravenous drug use. He recently quit smoking cigarettes; however he smoked one pack of cigarettes per day for the past 45 years.

On physical examination, his blood pressure was normal at 120/80 mm Hg and there was 3+ pitting edema of his lower extremities. The rest of the examination was unremarkable. At the time of presentation, serum creatinine was 0.9 mg/dL, serum albumin was 2.8 g/dL, total cholesterol was 290 mg/dL, and LDL cholesterol was 197 mg/dL. Liver function tests and complete blood count were normal. A 24-h urine collection revealed 8.5 g of protein. A work-up for secondary causes of nephrotic syndrome revealed normal complement levels. Hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, cryoglobulins, and human immunodeficiency virus (HIV) antibody were negative.

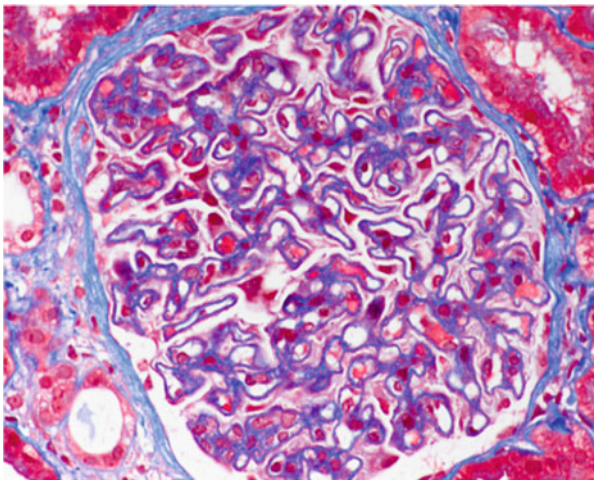

Fig. 3.1 Membranous Nephropathy (original magnification × 600, trichrome stain). Glomerulus displaying membranous features with fuchsinophilic subepithelial deposits. (Source: Jhaveri KD, Shah HH, Calderon K, Campenot ES, Radhakrishnan J. Glomerular diseases seen with cancer and chemotherapy: a narrative review. Kidney Int. 2013;84(1):34–44)

Serum and urine immunofixation did not reveal any monoclonal immunoglobulin. Sonogram revealed normal-sized kidneys. The patient was initially started on furosemide for edema management.

1. At this point, what would you do next?
   a. Kidney biopsy
   b. Start angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) and statins
   c. Check podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (anti-PLA2R) autoantibodies (if available)
   d. Start empiric oral corticosteroids

An ultrasound-assisted kidney biopsy was subsequently performed. Kidney biopsy revealed MN (Fig. 3.1).

2. What would you do next?
   a. Start or continue ACE-I or ARB therapy, statins
   b. Check anti-PLA2R autoantibodies (if available)
   c. Start sequential steroids and cytotoxic therapy
   d. Routine age- and sex-appropriate cancer screening
   e. Low-dose chest CT scan
   f. Call your pathologist to review kidney biopsy findings

MN remains the most common glomerular pathology reported in patients with solid tumors [2, 3]. The true prevalence of malignancy with MN is unknown. However, in 2006, Lefaucheur et al. reported a prevalence of malignancy of 10 % in their retrospective study of 240 patients with biopsy proven membranous nephropathy [4]. In this study, only half of the patients with malignancy-associated MN were known to have symptoms related to their cancer at the time of kidney biopsy [4]. However, most of these patients were diagnosed with malignancy within a year of

MN diagnoses. Several other case series have reported prevalence that ranges as low as 1 % to as high as 22 %. Zech et al. reported a prevalence of cancer as high as 22 % in their case series of MN patients who were older than 60 years [5].

The solid tumor malignancies most commonly associated with MN have been respiratory (lung and bronchus), and gastric carcinomas (Table 3.1). This is followed by renal carcinoma, prostate cancer, and thymoma. Breast cancer and other gastrointestinal cancers such as colorectal, pancreatic, esophageal, and hepatic have been also reported with MN. Tumors that have been rarely associated with MN include sarcoma, testicular seminoma, parotid adenolymphoma, adrenal ganglioneuroma, spinal schwannoma, and carotid body tumor.

Are there any clinical features, lab findings, or kidney biopsy findings that help to differentiate primary MN from secondary MN associated with solid tumors? Clinically, it is difficult to differentiate primary MN from secondary MN associated with solid tumors, especially when both types of MN present as nephrotic syndrome. However, in a known case of cancer, the presence of proteinuria or nephrotic syndrome should raise the possibility of underlying secondary type of glomerular disease. Similarly, the development of proteinuria or nephrotic syndrome within 12 months of the diagnosis of cancer should also increase the suspicion of underlying secondary form of glomerular disease, mainly cancer-associated MN. Lefaucheur et al. reported two risk factors that differentiate paraneoplastic MN from primary MN in their retrospective study of 240 patients with biopsy proven membranous nephropathy [4]. They include age over 65 years and history of smoking for more than 20 pack-years. Hence, one should consider cancer in patients with membranous nephropathy who are either older or have a long standing history of smoking. However, Beck in his article reviews the possibility of coincidental diagnosis of MN and cancer, especially in an older age group in which both diseases tend to occur [6]. In 2009, Beck et al. identified circulating autoantibodies to podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2R) in a majority of their cases of adult primary MN [7]. These autoantibodies were not found in cases of secondary MN. However, Qin et al. in their study did find elevated levels of anti-PLA2R autoantibodies in three out of ten MN patients with solid tumors [8]. Interestingly, all three MN patients with solid tumors and elevated levels of circulating anti-PLA2R autoantibodies had moderate glomerular immunoglobulin G4 (IgG4) deposition on kidney biopsy: A finding that has been described predominately in patients with primary MN. In comparison, all remaining seven patients with tumor-associated MN had no glomerular IgG4 deposition [8]. Clinically, all three MN patients with elevated levels of circulating anti-PLA2R autoantibodies also had either persistence or relapse of proteinuria, despite tumor resection, suggesting that these were patients likely with primary MN [8]. Recently, Hoxha et al. have also showed enhanced staining of PLA2 R in the glomeruli of patients with primary MN compared with normal staining in patients with tumor-associated MN [9]. As opposed to a predominant IgG4 subclass deposition in primary MN, Ohani et al. showed an increased glomerular deposition of IgG1 and IgG2 subtypes in patients with cancer-associated MN [10]. Hence, on the basis of the above data, the presence of circulating anti-PLA2 R antibodies and/or enhanced

Table 3.1 Glomerular diseases associated with solid tumors and hematologic malignancies. (Adapted from: Jhaveri KD, Shah HH, Calderon K, Campenot ES, Radhakrishnan J. Glomerular diseases seen with cancer and chemotherapy: a narrative review. Kidney Int. 2013;84(1):34–44)

Malignancy	Associated glomerular diseases reported in the literature
Lung cancer (includes small cell, non-small cell, squamous cell, and bronchogenic cancers)	MN, MCD, MPGN, IgAN, FSGS, CGN, HSP, TMA
Renal cell cancer	AAA, CGN, IgAN, MCD, FSGS, MPGN, HSP
Gastric cancer	MN, MPGN, CGN, HSP, TMA
Colon cancer	MN, MCD, CGN
Prostate cancer	MN, CGN, HSP
Bladder cancer	MCD
Pancreas cancer	MN, MCD, IgAN
Breast cancer	MN, FSGS, MPGN, HSP, TMA
Esophageal cancer	MPGN, FSGS
GI stromal cancer	AAA
Spleen sarcoma	AAA
Head and neck cancer	MN, IgAN
Wilms' tumor	MN, MPGN
Teratoma	MN
Ovarian cancer	MN, MCD
Cervical cancer	MN
Endometrial cancer	MN
Tongue cancer	IgAN
Mesothelioma	MCD
Melanoma	MN, MPGN
Skin cancer (basal and squamous cell cancers)	MN
Pheochromocytoma	MN
Thymoma	MCD, FSGS, CGN, MPGN
Hodgkin's lymphoma	MCD, MN, MPGN, IgAN, FSGS, CGN, AAA, Anti-GBM disease, HSP
Non-Hodgkin's lymphoma	MN, MCD, MPGN, IgAN, FSGS, HSP
Chronic lymphocytic leukemia	MPGN, MN, MCD, FSGS, CGN
Acute myelogenous leukemia	MN, FSGS
Chronic myelogenous leukemia	FSGS, MN, MCD, MPGN
MGUS	MPGN
T-cell leukemia	FSGS

AAA AA amyloidosis, *CGN* crescentic glomerlonephritis, *FSGS* focal segmental glomerulosclerosis, *GBM* glomerular basement membrane, *GI* gastrointestinal, *HSP* Henoch–Schonlein purpura, *IgAN* IgA nephropathy, *MCD* minimal change disease, *MGUS* monoclonal gammopathy of unclear significance, *MN* membranous nephropathy, *MPGN* membranoproliferative glomerulonephritis, *TMA* thrombotic microangiopathy

Table 3.2 Clinicopathologic parameters differentiating primary and solid tumor-associated MN. (Adapted from: Jhaveri KD, Shah HH, Patel C, Kadiyala A, Stokes B, Radhakrishnan J. Glomerular diseases associated with cancer, chemotherapy and hematopoietic stem cell transplantation. Adv Chronic Kidney Dis. 2014;21(1):48–55, with permission from Elsevier)

Clinicopathologic parameters	Primary MN	Solid tumor-associated MN
Historical clues	1. Younger age	1. Age over 65 years
	2. No history of smoking	2. Smoking for more than 20 pack years
Serological	Presence of circulating anti-PLA2R autoantibodies in serum	Absence of circulating anti-PLA2R autoantibodies in serum
Histopathological findings on kidney biopsy	1. Predominance of glomerular IgG4 deposition	1. Predominance of glomerular IgG1/IgG2 deposition
	2. Enhanced glomerular PLA2R staining	2. Normal glomerular PLA2R staining
	3. Presence of less than 8 inflammatory cells per glomeruli	3. Presence of more than 8 inflammatory cells per glomeruli

IgG immunoglobulin G, *MN* membranous nephropathy, *PLA2 R* phospholipase A2 receptor

glomerular PLA2 R staining with the predominance of IgG4 in the glomeruli of patients with MN are suggestive of primary MN even in the presence of cancer. In addition to the above, the presence of the increased inflammatory cells ($>$ 8 cells per glomeruli) on kidney biopsies was shown to be more suggestive of cancer-associated MN than primary MN, as reported by Lefachuer et al. [4]. However, more studies will need to confirm this finding.

Table 3.2 summarizes the above differentiating clinicopathologic parameters between primary and solid tumor-associated MN.

Although the above laboratory and kidney pathologic findings may herald cancer-associated MN, a high index of suspicion for underlying malignancy is also required when evaluating a case of MN in whom cancer is not yet diagnosed. The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group recently concluded that further studies are needed to determine the most cost effective panel of investigations for screening an underlying (covert) malignancy in the older patients with MN [11]. In the meantime, until such information is available, it is reasonable to perform routine age- and sex-appropriate screening for malignancy, once other known causes of secondary MN have been excluded. This may include fecal occult blood testing, colonoscopy, mammography, and prostate-specific antigen testing. In patients at high risk for lung cancer (for example, smokers), low-dose chest computed tomography (CT) should be considered. It is important to note that the risk of finding cancer may persist for at least 5 years from the time of kidney biopsy [12]. This prolonged risk period could be as a result of a slow-growing malignancy, use of cytotoxic therapy for MN, or due to increased surveillance [12]. Hence, close medical follow-up and evaluation are needed even if the cancer is not detected on initial screening done following the kidney biopsy findings.

The possible mechanisms whereby solid tumors may be associated with MN [6] include:

(a) In situ immune complex formation in which antibodies are formed against a tumor antigen that is localized in the subepithelial location, or to podocyte antigen that is identical or similar to the tumor antigen.
(b) Tumor antigens may form circulating immune complexes that are subsequently trapped in glomerular capillaries.
(c) External factors such as infections with oncogenic viruses or altered immune function that can cause both the malignancy and MN [6].

Case # 1 Follow-Up and Discussion
Testing for anti-PLA2R autoantibodies was not available, hence not sent. However, the pathologist was called to review the kidney pathology findings. It was also discussed with the pathologist that there was a high clinical suspicion for secondary form of MN, especially cancer-associated MN as our patient was above 65 years and had a strong personal history of smoking cigarettes. The patient also had significant (non-intentional) weight loss over the past several months. Interesting, further testing by the pathologist revealed a normal glomerular PLA2R staining, suggesting secondary form of MN. Patient subsequently underwent routine age- and sex-appropriate cancer screening and low-dose chest CT. He was found to have a right upper lung nodule on CT scan. A biopsy of the lung nodule revealed small cell lung cancer. The patient underwent partial lung resection followed by chemotherapy. A follow-up 3 months after the completion of his chemotherapy, revealed clinical and laboratory remission of nephrotic syndrome. Serum creatinine remained normal (0.9 mg/dL) and a 24-h urine collection revealed 0.3 g of protein.

Hematologic Malignancy-Associated MN

Hematological malignancies have been associated with MN [13, 14]. Chronic lymphocytic leukemia (CLL) has a much stronger association with membranoproliferative glomerulonephritis (MPGN), than with MN as reported in one case series [13]. However, Mallouk et al. found both MPGN (34 %) and MN (17 %) as the two most common glomerular lesions in their literature review of 53 cases with CLL and nephrotic syndrome [14]. The electron microscopy findings of fibrillary deposits on kidney biopsy may suggest an underlying hematological malignancy [13]. Both Hodgkin's and non-Hodgkin's lymphoma have also been associated with MN [14].

Minimal Change Disease (MCD)

Solid Tumor-Associated MCD

The solid tumor malignancies most frequently associated with MCD are lung, colorectal and renal cell cancers, and thymoma (Table 3.1). Pancreatic, breast, bladder, ovarian, and esophageal cancers have been rarely associated with MCD [2].

Hematologic Malignancy-Associated MCD

Case #2

A 21-year-old Hispanic male with no significant medical history presented to the emergency room with 10 days history of deteriorating bilateral lower extremity edema and 8-kg weight gain. He denied any past history of human immunodeficiency virus infection, hepatitis, or blood transfusion. There was no recent infection or travel history. He denied fever, chills, dyspnea, gross hematuria, arthralgias, or rash. Review of systems was otherwise negative. There was family history of kidney disease. There was no history of intravenous or recreational drug use. He also denied use of any medications, including NSAIDs and herbal medications.

On physical examination, his blood pressure was normal at 126/78 mm Hg, and there was 3+ pitting edema of his lower extremities. He also found to have a 2 × 2-cm right supraclavicular firm lymph node on examination. The rest of the examination was unremarkable. At the time of initial presentation, serum creatinine was 0.8 mg/dL, serum albumin was 1.8 g/dL, total cholesterol was 390 mg/dL, LDL cholesterol was 267 mg/dL, and triglycerides was 402 mg/dL. Liver function tests and complete blood count were normal. Urinalysis was significant for 5–10 RBC/hpf and 3+ proteinuria. A 24-h urine collection during hospital stay revealed 12.5 g of protein. The patient was initially started on furosemide for edema management. A work-up for secondary causes of nephrotic syndrome revealed normal complement levels. Hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, cryoglobulins, and human immunodeficiency virus (HIV) antibody were negative. Serum and urine immunofixation did not reveal any monoclonal immunoglobulin. Sonogram revealed normal-sized kidneys. The patient was initially started on furosemide for edema management. A kidney biopsy was subsequently performed in this case. Kidney biopsy revealed MCD.

At this point, what would you do next?

a. Start ACE-I or ARB, statins
b. Start high-dose corticosteroids
c. Lymph node biopsy

Hematologic malignancies such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, and chronic leukemias have been associated with MCD. Of all the lymphoid malignancies, MCD has been classically associated with Hodgkin's lymphoma. However, the incidence of nephrotic syndrome is low in this group and is estimated to be around 0.5–1 % [15].

MCD usually presents in most patients around the time the malignancy is diagnosed. However, in one case series, the diagnosis of MCD preceded the diagnosis of Hodgkin's lymphoma by several months in 8 (38.1 %) of the 21 patients studied [15]. In the remaining 13 cases, the diagnosis of MCD was made either simultaneously (4 cases) or after (9 cases) the diagnosis of Hodgkin's lymphoma. In this case series, over two thirds of patients with Hodgkin's lymphoma and MCD had systemic symptoms (fever, weight loss, and night sweats), and 90 % showed markers of an inflammatory syndrome (as assessed by C-reactive protein level, sedimentation rate, and fibrinogen levels) [15]. Nodular sclerosing was the predominant morphological subtype seen in over two thirds (71.4 %) of Hodgkin's lymphoma patients [15].

Hodgkin's lymphoma-associated MCD may also be associated with a higher frequency of steroid and cyclosporine resistance [15]. Hence, a poor response to the treatment of MCD should prompt an investigation for an underlying lymphoma. In the above case series, the simultaneous diagnosis of Hodgkin's lymphoma and MCD was associated with the complete remission of nephrotic syndrome after chemotherapy [15]. Nephrotic syndrome usually relapses simultaneously with the hematologic malignancy; however, it remains highly responsive to specific cancer treatment. MCD can also occur at the time of cancer relapse even if it was initially absent, emphasizing the need to evaluate proteinuria during the follow-up of patients with Hodgkin's lymphoma.

Case # 2 Follow-Up and Discussion

Patient underwent right supraclavicular lymph node biopsy that revealed nodular sclerosing Hodgkin's lymphoma. A subsequent staging evaluation involving chest/abdomen/pelvic CT, positron emission tomography (PET) scan, and a bone marrow biopsy revealed stage 2A Hodgkin's lymphoma.

Approximately 4 weeks after his initial evaluation, the patient received the first cycle of chemotherapy, consisting of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). A 24-h urine collection prior to chemotherapy revealed 12 g protein. The patient tolerated chemotherapy well. He was continued on oral furosemide therapy. Two weeks after induction chemotherapy, the patient showed a significant improvement of his lower extremity edema. Six weeks after receiving chemotherapy, the patient continued to show further improvement of his lower extremity edema, and had a complete resolution of his supraclavicular lymphadenopathy. His diuretic therapy was subsequently discontinued. At 6-month follow-up, his spot urine total protein to creatinine ratio decreased to 0.3. His serum albumin increased to 4 mg/dL and serum creatinine remained in normal range.

Thymoma-Associated Glomerular Diseases

The most common glomerular disease associated with thymoma is MCD [16]. Karras et al. studied 21 cases of thymoma-associated nephropathy. Majority of the cases are presented with nephrotic syndrome, and 50 % of their cases also had renal failure. They also reviewed 21 additional cases previously reported in the literature [16]. Majority of the thymoma-associated nephropathy cases in this study had MCD followed by MN. Other glomerular diseases included focal segmental glomerulosclerosis (FSGS), crescentic glomerulonephritis (CGN), and lupus nephritis [16]. It is interesting to note that thymoma-associated MCD in this study had a distinct clinical presentation from thymoma-associated MN. In most cases, MCD was diagnosed after the thymoma was treated successfully while MN was diagnosed with either newly diagnosed or recurrent thymoma [16]. Treatment of the malignancy resulted in rapid improvement of the nephrotic syndrome in MN cases. Majority of the patients with MCD received high-dose steroids with varying responses [16].

Focal Segmental Glomerulosclerosis (FSGS)

Solid Tumor-Associated FSGS

Solid tumor malignancies have rarely been associated with FSGS. The most frequently reported cancers that have associated with FSGS include renal cell carcinomas and thymoma. Less frequent reported association includes lung, breast, and esophageal cancers [2].

Hematologic Malignancy-Associated FSGS

FSGS has been associated with Hodgkin's lymphoma, however its occurrence is much less than that of MCD [14]. Mallouk et al. reported a case of Hodgkin's-associated FSGS and also reviewed six additional cases that were reported previously in the literature [14]. All seven patients responded well to chemotherapy for Hodgkin's lymphoma and showed significant improvement in degree of proteinuria and renal function [14].

Although rare, glomerular diseases presenting as nephrotic syndrome have been associated with the hemophagocytic syndrome (HPS) secondary to malignancy. Thaunat et al., in their study, identified 11 patients with HPS that developed nephrotic syndrome [17]. Of the 11 patients, 6 had lymphoma (Hodgkin's: 1, T cell: 4, B cell: 1) as the etiology of HPS. Acute kidney injury was also present in all of these six cases. Kidney biopsy of these six cases revealed collapsing glomerulopathy (with negative human immunodeficiency virus serology) in four cases and MCD in two

cases. Interesting, five of these six patients were of Black African descent. Four of these six patients died of either severe HPS or underlying lymphoma [17].

An FSGS-like pattern of glomerular injury has been associated with myeloproliferative neoplasms (MPN) such as chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Au et al. in their retrospective study of 138 patients with MPN found five patients (3.6 %) with FSGS and diffuse mesangial sclerosis on kidney biopsy [18]. These patients presented with proteinuria and two progressed to chronic kidney disease. Said et al. studied eleven patients with MPN (PMF: 8, CML:1, PV: 1 and ET:1) who developed proteinuria and kidney failure [19]. The most common clinical presentation of MPN-associated glomerulopathy, in this case series, was nephrotic-range proteinuria and chronic kidney disease. Proteinuria was often present for some time (mean 2 years) before kidney biopsy. Kidney biopsies of these eleven patients showed mesangial sclerosis with hypercellularity in all patients, segmental sclerosis in eight patients, features of thrombotic microangiopathy (TMA) in eight patients, and intracapillary hematopoietic cells infiltration in four patients [19]. MPN-associated glomerulopathy was found to a late complication of the underlying malignancy and had a poor prognosis with progressive kidney disease in most patients [19]. Plasma and urine levels of platelet-derived growth factor are elevated in patients with MPN and have been shown to induce glomerulosclerosis, mesangial proliferation, and fibrosis [20, 21]. In some patients, partial remission of the FSGS was seen with treatment of the underlying disease [18, 22, 23].

Membranoproliferative Glomerulonephritis (MPGN)

Solid Tumor-Associated MPGN

MPGN has been described in association with various solid tumor malignancies. The solid malignancies associated with MPGN include lung, kidney, and stomach cancers [2]. Rare associations have been described with melanoma, breast cancer, and thymoma [2].

Hematologic Malignancy-Associated MPGN

Case # 3
A 62-year-old white male with long standing history of hypertension and recent history of CLL was referred by his oncologist for evaluation of proteinuria and elevated serum creatinine. He denied any past history of diabetes, hepatitis, or

blood transfusion. There was no recent infection or travel history. Review of systems was significant for bilateral intermittent lower extremity swelling over the past 4 months. He denied fever, chills, dyspnea, gross hematuria, arthralgias, or rash. His current medication included amlodipine for hypertension management. He also denied use of any other medications, including NSAIDs and herbal medications. There was no history of recreational or intravenous drug use.

On physical examination, his blood pressure was elevated at 160/94 mm Hg. There was a mild edema of his lower extremities. The rest of the examination was unremarkable. At the time of presentation, serum creatinine was 1.5 mg/dL and serum albumin was 3.5 g/dL. Complete blood count, liver function tests, and lipid profile were normal. Urinalysis was significant for 10–20 RBC/hpf and 2+ proteinuria. A 24-h urine collection revealed 1.8 g of protein. A work-up for secondary causes of proteinuria revealed low C3 and C4 levels. Hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, cryoglobulins, and human immunodeficiency virus (HIV) antibody were negative. Serum and urine immunofixation did not reveal any monoclonal immunoglobulin. Sonogram revealed normal-sized kidneys. A kidney biopsy was subsequently performed.

1. What is the most likely kidney biopsy diagnosis?
   a. MN
   b. MPGN
   c. FSGS
   d. Acute interstitial nephritis

MPGN is the most common pattern of glomerular injury seen in patients with CLL [2]. Unlike Hodgkin's lymphoma, which presents as MCD, other B cell diseases such as CLL, hairy cell leukemia, and non-Hodgkin's lymphoma usually present with MN and MPGN [24].

Da'as et al. described the kidney biopsy findings in their case series of five patients with lymphocytic leukemia and/or non-Hodgkin's lymphoma [24]. They found two patients with MPGN. The remaining three patients had either MN, diffuse proliferative glomerular disease, or infiltrative disease. In addition, they also reviewed 42 previously reported cases of glomerular diseases in the literature that were associated with CLL [24]. Out of these 42 patients, 36 had nephrotic-range proteinuria, with the most common glomerular lesion being MPGN followed by MN [24].

Moulin et al. studied thirteen patients with glomerular diseases associated with either CLL (11 cases) or well-differentiated lymphocytic lymphoma (2 cases) [13]. Out of 13 patients, 9 had nephrotic syndrome and the remaining four patients had subnephrotic proteinuria. Kidney biopsies revealed a MPGN pattern of injury in eight patients and the rest had either MN, FSGS, mesangial hypertrophy, advanced

sclerosing, or CGN. Five out of the eight MPGN patients also had cryoglobulinemia [13]. Out of these 13 patients, 10 received chemotherapy. Seven of these ten treated patients received oral chlorambucil-based chemotherapy. Among the seven treated patients with nephrotic syndrome, six patients achieved complete remission of nephrotic syndrome and one achieved partial remission. Seven patients also had an improvement in renal function [13].

MPGN on kidney biopsy may also be a clue to an underlying undiagnosed or developing lymphoplasmacytic malignancy. Sethi et al. reported a possible association between MPGN and monoclonal gammopathy. [25]. Twenty-eight patients with hepatitis-negative MPGN and monoclonal gammopathy who underwent bone marrow biopsies were analyzed. Of the 28 cases, 16 were classified as monoclonal gammopathy of uncertain significance (MGUS). Of the remaining 12 cases, bone marrow showed CLL (2 cases), lymphoplasmacytic lymphoma (one case), low-grade B cell lymphoma (3 cases) or multiple myeloma (6 cases). While two cases with MGUS subsequently converted to multiple myeloma, another case of MGUS converted to CLL [25]. It has to be noted that there has been no proven relationship between the presence of monoclonal protein and the development of MPGN. Although current observations suggest this possibility, more studies are needed to prove the plausibility of such association.

Case #3 Follow-Up and Discussion
Kidney biopsy findings were consistent with MPGN (Fig. 3.2). Patient was treated with chemotherapy for CLL. After a 6-month follow-up, his spot urine total protein to creatinine ratio normalized to 0.2. His serum albumin increased to 4.1 mg/dL and serum creatinine improved to 1.0 mg/dL.

IgA Nephropathy (IgAN)

Mustonen et al., in 1984, reported the first known association between IgAN and solid tumors of the respiratory tract, the buccal mucosa, and the nasopharynx [26]. Treatment of the underlying tumor was shown to improve IgAN [26]. However, since then, renal cell carcinoma has been the most frequently reported solid tumor malignancy that has been associated with IgAN [27]. A case of IgAN has been associated with cutaneous T-cell lymphoma [28].

Henoch–Schonlein Purpura (HSP)

Although rare, both solid tumors (lung, prostate, breast, renal, gastric, small bowel) and hematological malignancies (multiple myeloma, non-Hodgkin's lymphoma,

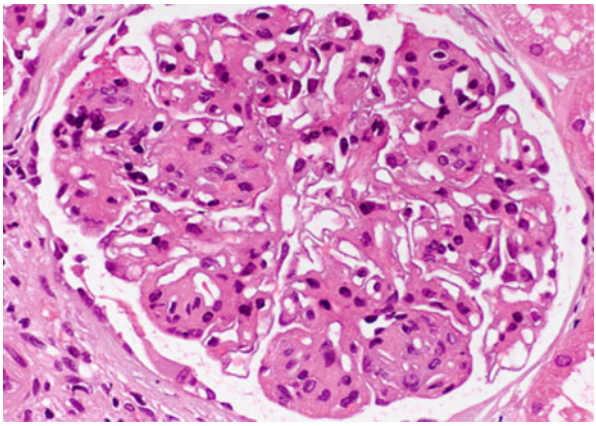

Fig. 3.2 Membranoproliferative glomerulonephritis (original magnification × 600, hematoxylin and eosin (H&E) stain). Glomerulus displaying membranoproliferative features with accentuated lobularity, mesangial proliferation, and endocapillary proliferation. (Source: Jhaveri KD, Shah HH, Calderon K, Campenot ES, Radhakrishnan J. Glomerular diseases seen with cancer and chemotherapy: a narrative review. Kidney Int. 2013;84(1):34–44)

Hodgkin's lymphoma, myeloproliferative disease) have been associated with adult HSP [29, 30]. The majority of patients (55 %) in a study developed HSP within 1 month of cancer diagnosis or detection of metastases [30]. Older age and male gender has been reported as risk factors for identifying patients with underlying cancer-associated HSP [30].

Crescentic Glomerulonephritis (CGN)

CGN has been associated with several solid tumor malignancies, including renal cell cancers and gastric and lung cancers [3]. In 1984, Biava et al. described non-renal malignancy in association with pauci-immune CGN before the discovery of antineutrophil cytoplasmic antibodies (ANCA) [31]. Treatment with standard therapy of steroids and cyclophosphamide resulted in partial or complete remission [31]. It is not yet established whether the removal of tumor alone treats the vasculitic process. Moreover, although patients with ANCA-associated vasculitis may be at higher risk for developing cancers than the general population, some of these cancers may be related to the immunosuppressive medications given for the treatment of vasculitis [32]. Anti-glomerular basement membrane disease has also associated with Hodgkin's disease [33].

Thrombotic Microangiopathy (TMA)

TMA has been reported in patients with mucin-producing gastric, lung, and breast cancers [34]. Cancer-associated TMA has a poorer response to plasmapheresis compared with TMA associated with other conditions. This could be because the activity of ADAMTS13 (a serum protease that breaks down multimeric Von Willebrand's factor) is not severely impaired [35]. Clinically, a poor response to plasma exchange therapy could be an important clue for investigating malignancy as a cause of TMA. It has also been shown that cancer-related TMA carries a poorer prognosis as compared with TMA related to nonmalignant conditions [34]. This poorer prognosis of cancer-associated TMA is often because of the presence of metastatic disease with microvascular tumor emboli or bone marrow tumor invasion.

Fibrillary and Immunotactoid Glomerulonephritis

Fibrillary glomerulonephritis (FGN) and immunotactoid glomerulopathy (ITG) belong to the group of rare renal disorders characterized by organized fibrillar or microtubular glomerular deposits. ITG is tenfold less common than FGN [36, 37]. These rare glomerular diseases could either present as a primary condition or be associated with other medical conditions including malignancy [36, 37]. Although thought to be an idiopathic condition [36], a more recent single institution study of 66 cases with FGN found an association with malignancy in 15 (23 %) patients [37]. Out of these 15 cases with FGN and malignancy, 6 had multiple myeloma. The remaining nine cases had non-hematologic malignancies that included thyroid, hepatocellular, breast, uterine, prostate, colon, renal cell cancers, and melanoma [37]. As no tumor antigens have been shown in the glomerular fibrillar deposits, the pathogenetic link between FGN and cancer remains unclear [37]. ITG has been associated with lymphoproliferative disorders including CLL [36]. Hence, a diagnosis of these rare glomerular diseases on kidney biopsy should warrant an investigation of an underlying malignancy.

Summary

Both solid tumors and hematological malignancies have been associated with glomerular diseases. Pathogenesis of most cancer-associated glomerular diseases remains poorly understood. Knowledge and approach to these paraneoplastic glomerular diseases is important for both the nephrologists and cancer specialists. Failure to recognize cancer-associated glomerular diseases may lead to the use of unnecessary therapies. The treatment of cancer-associated glomerular diseases is targeted at the cause, namely treating the underlying cancer. Further studies are required to understand the pathogenesis of cancer-associated glomerular diseases.

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Chapter 4
Nephrotoxicity of Chemotherapy Agents

Aziz K. Valika and Anushree Shirali

List of Abbreviations

ADH	Antidiuretic hormone
ADT	Androgen deprivation therapy
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ALK	Anaplastic lymphoma kinase
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CNS	Central nervous system
DI	Diabetes insipidus
DHFR	Dihydrofolate reductase
EGF	Epidermal growth factor
FS	Fanconi syndrome
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
HTN	Hypertension
INF	Interferon
MCD	Minimal change disease
MHC	Major histocompatibility complex
MPGN	Membranoproliferative glomerulonephritis
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
NS	Nephrotic syndrome
OCT	Organic cationic transporters
RNR	Ribonucleotide reductase
RSWS	Renal salt wasting syndrome

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RTA	Renal tubular acidosis
RTEC	Renal tubular epithelial cells
SIADH	Syndrome of inappropriate antidiuretic hormone
TMA	Thrombotic microangiopathy
TNF	Tumor necrosis factor
TRPM	Transient receptor potential melastin
VEGF	Vascular endothelial growth factor

Chemotherapy agents aim to improve the survival of cancer patients yet many have the potential for inducing systemic toxicity, including toxicity which affects the kidneys. Renal toxicity, mostly in the form of acute kidney injury (AKI), can delay or prevent continuation of chemotherapy and can lead to a number of clinical renal syndromes that are associated with significant morbidity and mortality. Thus, preventive measures against nephrotoxicity, prompt recognition of kidney injury in its early stage, and well-defined interventions against established nephrotoxicity are critical steps in limiting adverse patient outcomes related to chemotherapy-induced nephrotoxicity. This chapter highlights the risk factors for chemotherapy-associated nephrotoxicity and examines the commonly encountered clinical renal syndromes in this setting.

Risk Factors for Nephrotoxicity of Chemotherapy Agents

The nephrotoxic potential of chemotherapy agents is dependent on factors specific to the kidney, drug, and patient (Fig. 4.1). Although even a single factor such as hypovolemia may be enough to precipitate kidney injury, nephrotoxicity commonly manifests itself when there is convergence of multiple risk factors. Since the kidney receives 25 % of the cardiac output and filters many drugs, it is inherently vulnerable to toxicity from high drug concentration. Renal tubular epithelial cells (RTEC) are particularly at risk as they are exposed to increased drug concentrations via peritubular capillary blood flow as well as via ultrafiltrate [1]. Organic cationic transporters (OCTs) and organic anionic transporters (OATs) facilitate drug entry into RTEC and subsequently, apical efflux transports drugs into tubular lumens [1]. Agents that are filtered at the glomerulus gain entry to RTEC at the apical surface through endocytosis or pinocytosis [1]. Both pathways of drug delivery expose RTEC to potentially high concentrations of nephrotoxic drugs. RTEC in the loop of Henle are particularly at risk for nephrotoxic injury because their high metabolic activity from solute transport generates a hypoxic microenvironment. Additional metabolic tasks include drug modification via enzyme systems such as cytochrome p450, which generate toxic metabolites and reactive oxygen species, both of which may injure kidney parenchymal cells. The kidney microenvironment plays a pivotal role in the nephrotoxic potential of specific drugs. This is well illustrated with methotrexate (MTX)-induced kidney injury. As discussed later, crystal precipitates of MTX and metabolic derivatives are critical to the tubular injury induced by this drug. Acidic pH is a critical risk factor for MTX to precipitate into crystals [2]. Urine pH is generally in

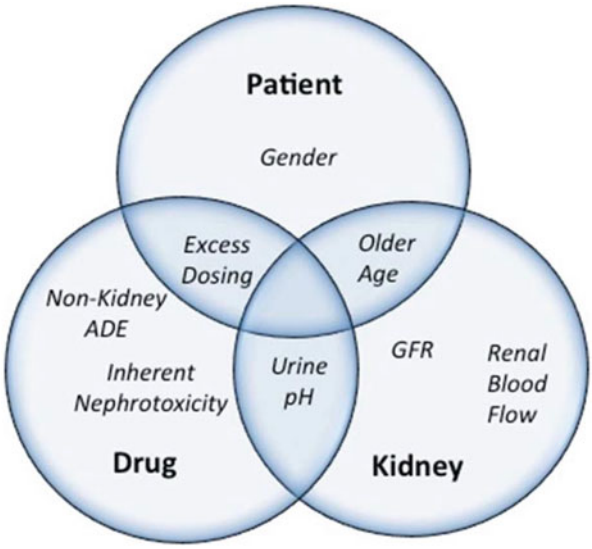

Fig. 4.1 Risk of chemotherapy-associated *AKI* depends on the interactions among patient, drug, and kidney specific risk factors. *ADE* adverse drug effects, *AKI* acute kidney injury, *GFR* glomerular filtration rate

the acidic range especially if the diet is rich in protein. Thus, without alkalinization to raise urinary pH, MTX and its related compounds are likely to precipitate and lead to crystal-induced kidney injury.

In addition to kidney- and drug-specific risk factors, patient characteristics are critical in understanding how chemotherapy drugs affect the kidney. For example, the risk for excessive drug dosing is higher in older and female patients because they have reduced total body water and excessive serum drug concentrations may occur in this population. Additionally, decreased muscle mass in these patients results in lower creatinine, which may be misinterpreted as preserved or normal glomerular filtration rate (GFR) rather than reduction of muscle mass. One approach that may reduce excessive dosing in these patients is to base chemotherapy dosing on measured rather than estimated creatinine clearance. If that is not feasible, use of estimating equations for GFR other than Cockcroft–Gault may be more precise. While there is scant data examining the accuracy of various estimating equations, one retrospective study found that the Wright equation was superior to Cockcroft–Gault in accurately calculating GFR (using [^{51}Cr]-ethylenediamine tetraacetic acid measured clearance as the standard) [3].

Comorbidities in the cancer patients also influence the development of nephrotoxicity. These may include cirrhosis and congestive heart failure, which result in a functional prerenal state via decreased effective circulating volume. Adverse nonrenal side effects of chemotherapy including vomiting and diarrhea similarly predispose the cancer patient to kidney injury via creating a prerenal state. Furthermore, certain types of cancers are associated with higher proclivity for renal injury. For example, patients who have malignancies affecting the biliary system may also have obstructive jaundice, which may lead to renal hypoperfusion and bile salts-related tubular toxicity. Malignancies of the hematopoietic system such as leukemia and lymphoma may cause kidney injury directly via infiltration into renal parenchyma or indirectly via

tumor lysis syndrome. Finally, paraproteinemic disorders such as multiple myeloma induce a diverse spectrum of kidney disease including amyloidosis, light and heavy chain deposition, and cast nephropathy. In patients with the aforementioned cancers, additional risk factors for nephrotoxicity compound the propensity for adverse renal drug effects.

Clinical and Pathological Classification of Nephrotoxicity from Chemotherapy Agents

Chemotherapy agents can cause kidney disease that fits the traditional grouping into prerenal, intrarenal, and postrenal states. However, most of these agents cause intrinsic renal injury at various parts of the nephron (Fig. 4.2), with a couple of notable exceptions. For example, interleukin-2 (IL-2) is associated with capillary leak syndrome, which can cause intravascular volume depletion and prerenal azotemia. Postrenal injury is rare with chemotherapy agents but case reports have linked cyclophosphamide with bladder outlet obstruction from vesicular thrombi in the setting of hemorrhagic cystitis [3]. In the following sections, we discuss intrarenal injury from chemotherapy agents common in current clinical practice, using a case-based approach to highlight clinical syndromes of acute tubular necrosis (ATN), tubulopathies, vascular injury, glomerular disease, acute interstitial nephritis (AIN), and crystal nephropathy (Fig. 4.2, Table 4.1).

Acute Tubular Necrosis (ATN)

Case #1
A 66-year-old male has a history of hypertension (HTN) and chronic kidney disease (CKD), with baseline creatinine of 1.5 mg/dL. He is diagnosed with stage IV non-small cell lung cancer and is initiated on therapy with cisplatin, bevacizumab, and pemetrexed. Bevacizumab is discontinued after one cycle due to the development of a stomach ulcer. Cisplatin and pemetrexed are continued for seven more cycles. During the most recent infusion, the patient develops the following laboratory abnormalities: creatinine of 2.2 mg/dL, BUN of 37 mg/dL, bicarbonate of 20 meq/L, and potassium of 4.5 meq/L. Urinalysis shows no proteinuria but a urine microscopy shows granular casts and RTEC. Urinary sodium is 35 meq/L. A kidney sonogram reveals no hydronephrosis.

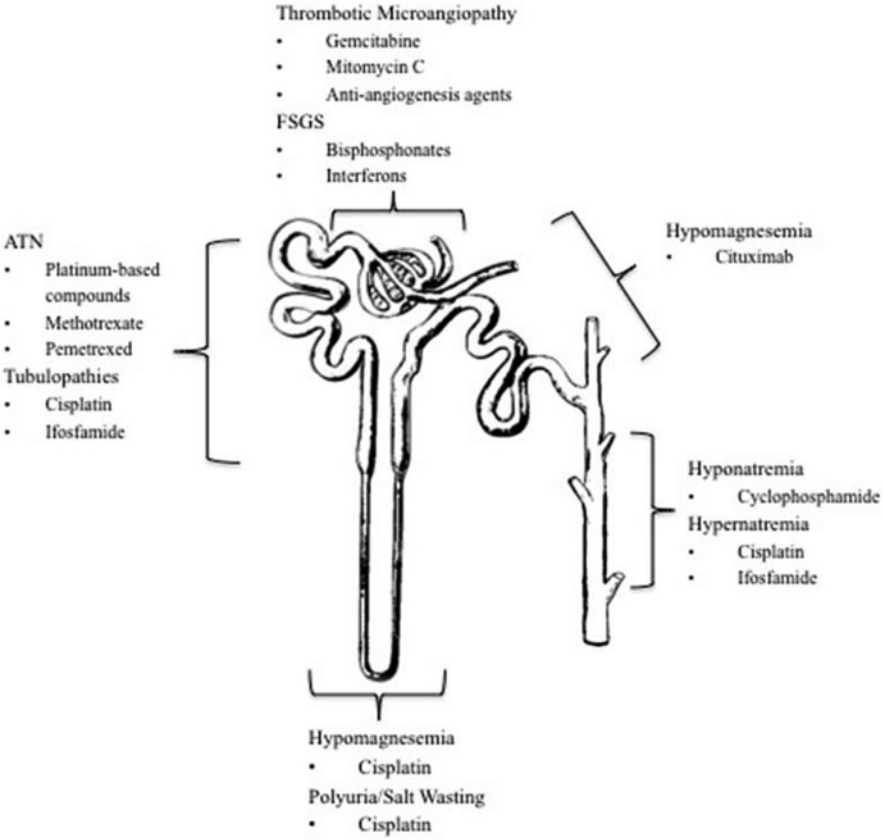

Fig. 4.2 Chemotherapy-associated nephrotoxicity acts on each part of the nephron to produce distinct clinical syndromes. *ATN* acute tubular necrosis, *FSGS* focal and segmental glomerulosclerosis

Which one of the following is true?

a. Furosemide or mannitol given in addition to saline is proven to decrease the risk of AKI in cisplatin treatment
b. The basolateral OCT-2 channel may mediate the tubular injury seen with both cisplatin and ifosfamide.
c. This patient's baseline renal insufficiency is not a risk factor for AKI due to cisplatin treatment
d. Substituting oxaliplatin or carboplatin for cisplatin would not have reduced his risk for AKI
e. Only pemetrexed is a likely cause for this patient's AKI

Table 4.1 Clinical syndromes of nephrotoxicity associated with chemotherapy agents

ATN	**Tubulopathies**	**Renal vasculature**	**AIN**
Platinum agents	*Fanconi syndrome*	*Hemodynamic AKI (capillary leak)*	Ipilimumab, tremelimumab
Ifosfamide	Ifosfamide	IL-2	Sorafenib
Pemetrexed	Cisplatin	Denileukin diftitox	Sunitinib
Imatinib	Azacitidine	*TMA*	
Mithramycin	Imatinib	Antiangiogenesis agents (VEGF and tyrosine kinase inhibitors)	
Pentostatin	Pemetrexed	Gemcitabine	
Zoledronate	Diaziquone	Cisplatin	
Diaziquone	*RSW*	Mitomycin C	
	Cisplatin	IFN	
	Azacitidine		
	Magnesium wasting		
	Cetuximab		
	Panitumumab		
	Cisplatin		
	SIADH		
	Cyclophosphamide		
	Vincristine		
	NDI		
	Cisplatin		
	Ifosfamide		
	Pemetrexed		
CKD	**Nephrotic syndrome**	**Urinary tract and crystal nephropathy**	**Prerenal**
Nitrosoureas, Ifosfamide	Minimal change disease	Methotrexate	Interleukin-2
	Interferon α, β, γ	Cyclophosphamide	(Capillary Leak Syndrome)
	FSGS	(hemorrhagic cystitis)	
	Interferon α, β, γ		
	Pamidronate, zoledronate (rare)		

AKI acute kidney injury, *RSW* renal salt wasting, *ADH* antidiuretic hormone, *SIADH* syndrome of inappropriate antidiuretic hormone, *NDI* nephrogenic diabetes insipidus, *AIN* acute interstitial nephritis, *CKD* chronic kidney disease, *FSGS* focal segmental glomerulosclerosis, *VEGF* vascular endothelial growth factor *TMA* thrombotic microangiopathy, *IL-2* interleukin-2, *ATN* acute tubular necrosis, *IFN* interferon

As noted above, some drugs used for the treatment of malignancies cause direct injury to the cells of the renal tubules (Fig. 4.2), resulting in cellular death and ATN. Several chemotherapy drugs are implicated in causing ATN (Table 4.1). Depending on the particular drug or the severity and duration of injury, renal recovery may not be complete and result in CKD. Clinically, ATN presents with a rise in creatinine and decline in GFR. Tubular sodium reabsorption may be compromised, and a high urine sodium or FeNa > 2 % thus helps distinguish ATN from a prerenal insult. Microscopy may reveal RTEC and either granular or RTEC casts. Occasionally, severe injury can result in oliguric AKI, necessitating renal replacement therapy.

Cisplatin

Of the many drugs reported to cause ATN, cisplatin is the most well-known and best-studied nephrotoxic chemotherapy agent. It has been one of the oldest and the most frequently used platinum-based compounds in the treatment of cancer [4], and its effect on the kidney is a prototype for chemotherapy-induced nephrotoxicity. Cisplatin is known to cause dose-dependent ATN in up to one third of the patients receiving therapy [4], and appears to exert its deleterious effect mainly on proximal tubular cells. The kidney serves as the principal pathway for cisplatin excretion from the body, and the drug tends to accumulate in the kidney more so than other organs. Cells of the proximal tubule uptake cisplatin via OCT-2 [5], which leads to drug accumulation within proximal renal tubular cells that is five times greater than serum concentration [6]. This accumulation of cisplatin and its metabolites explains the drug's preference for toxicity and damage to proximal tubule cell [7]. Most commonly, this injury results in tubular necrosis with AKI but as discussed later, an isolated proximal cell tubulopathy with acidosis and electrolyte abnormalities can also develop.

Cisplatin-induced nephrotoxicity is mediated through several pathways, including oxidative stress injury, upregulation of inflammatory mediators, and triggering of cell apoptosis [8]. The primary step occurs when a chloride ion on the parent drug is hydrolyzed and releases free hydroxyl radicals [4]. Through this and various other pathways, the production of reactive oxygen species is upregulated in cisplatin-exposed tubular cells. The resulting free radicals are directly toxic to various cell structures and promote apoptosis [6]. Inflammatory changes that occur include enhanced renal expression of tumor necrosis factor-alpha (TNF-apha), a potent pro-inflammatory molecule. TNF-alpha, along with mitogen-activated protein kinase and p53, leads to kidney injury via apoptosis [4], and further production of cytokines, chemokines, and reactive oxygen species [6]. Apoptosis also occurs through other mechanisms, including activation of initiator caspases through mitochondrial dysfunction and oxidative stress. A direct effect of cisplatin on caspase 1 which activates caspase 3, a final pathway in the apoptosis cascade, may also contribute [8]. Finally, cisplatin therapy may also decrease renal blood flow via damage to the renal vasculature, resulting in direct ischemic or hypoxic effects to the proximal tubule. Other platinum-based drugs appear to carry less of a risk for nephrotoxicity. In in

vitro studies, carboplatin and oxaliplatin display no affinity for OCT-2, and both lack chloride ions on their stem [5, 9, 10]. However, in high cumulative doses and in patients with the appropriate risk factors, there is still an appreciable risk of ATN from these newer derivative platinum drugs [[11]T, [12]].

The management of cisplatin-induced renal injury is centered on prevention. Volume repletion, usually with isotonic saline, is a standard treatment. Once ATN has occurred, avoiding further dosing of the drug is key, and the concomitant use of other potential nephrotoxins should be strictly avoided. Though diuretics have been used to increase urine flow as a prophylactic strategy, a randomized control trial by Santoso et al. comparing saline alone, furosemide with saline, and mannitol with saline, was closed early due to a trend toward increased AKI in the mannitol group [13]. There was no difference at the time between the subjects receiving furosemide compared to saline alone [13]. Other strategies to reduce AKI include the glutathione analog amifostine and sodium thiosulfate, which may protect against free radical injury [14]. However, use of these drugs is currently limited in clinical practice due to the lack of rigorous clinical data regarding their efficacy, significant side effects and cost of these drugs, and persistent concern that their use may hinder the antitumor effect of cisplatin. Several other agents studied in animals have not yet made it into clinical practice (nucleophilic sulfur thiols, neurotrophins, phosphonic acid, melanocortins, and free oxygen radical scavengers) [15]. Chemical substrates such as cimetidine compete with cisplatin for uptake via OCT-2, and have been suggested as therapeutic interventions to prevent intracellular concentration in the proximal tubule cells, but thus far there is a lack of clinical studies targeting this mechanism.

Ifosfamide

Similar to cisplatin, ifosfamide and its metabolites are known to be directly toxic to the cells of the proximal tubule. It is an alkylating agent commonly used for the treatment of several different solid organ tumors, as well as certain lymphomas and sarcomas. Renal toxicity occurs in up to 30 % of those on treatment [16], but unlike cisplatin, AKI is less frequent, and the more common manifestation is Fanconi syndrome (FS) or an isolated proximal renal tubular acidosis (Type 2 RTA) [17].

Unlike its parent drug, cyclophosphamide, ifosfamide (Fig. 4.2) produces the nephrotoxic metabolite chlorocetaldehyde. The kidney may be more susceptible to injury from ifosfamide and its metabolite because the cytochrome p450 enzymes that are responsible for the metabolism of ifosfamide are highly expressed in the kidney [18]. Furthermore, similar to cisplatin, ifosfamide is actively transported into the tubular cells via the basolateral transporter OCT-2, whereas cyclophosphamide is not, again suggesting a possible therapeutic target for renal injury prevention [19]. Despite this, the overall risk of AKI is less when compared to cisplatin. A cumulative lifetime dose of greater than 60–80 g/m^2 is associated with an increased risk for nephrotoxicity, but renal injury may happen at lower levels as well. Prior cisplatin use may also be an independent risk factor for injury [20]. Mesna, which is commonly used to prevent hemorrhagic cystitis, does not help to prevent AKI [16].

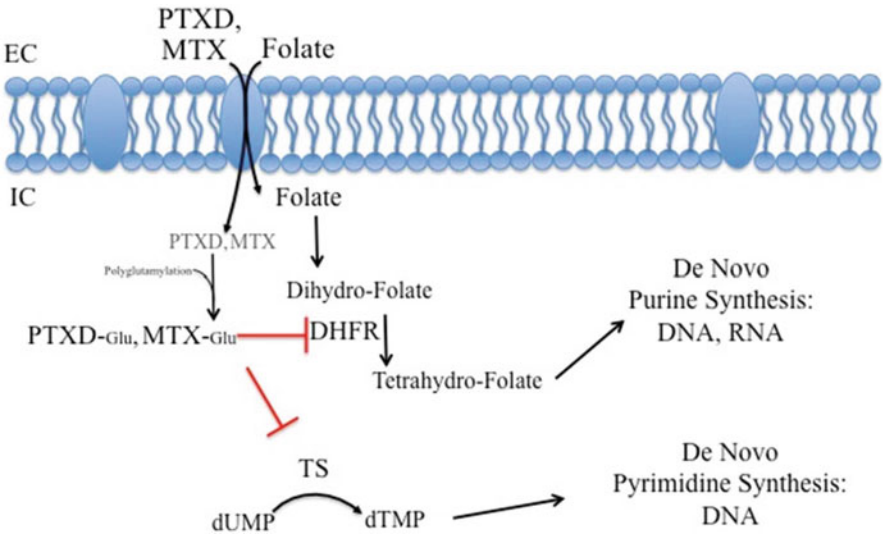

Fig. 4.3 Simplified schema illustrating effect of methotrexate (*MTX*) and pemetrexed (*PTXD*) on enzymes involved in de novo purine and pyrimidine metabolism. *DHFR* dihydrofolate reductase, *dTMP* deoxythymidine monophosphate, *dUMP* deoxyuridine monophosphate, *EC* extracellular, *IC* intracellular, *TS* thymidylate synthase

Not much is known about the mechanism of ifosfamide toxicity, but its effect on long-term renal function and the development of CKD will be discussed later.

Pemetrexed

An antifolate agent that is a structural analogue of MTX, pemetrexed acts to inhibit enzymes involved in purine and pyrimidine metabolism, thus interfering with the DNA and RNA synthesis which is necessary for cell replication of rapidly dividing tumor cells. It is used commonly for malignancies such as mesothelioma and non-small cell lung cancer among others. Uptake into proximal tubule cells occurs via both apical folate receptor-α transporters and basolateral-reduced folate carriers, and once in the cells, pemetrexed becomes trapped by polyglutamylation (Fig. 4.3) [15]. Increasing intracellular concentrations lead to further inhibition of folate metabolism, and likely contribute to renal tubular cell injury. Thus, both the toxicity and therapeutic effect of pemetrexed are tied to its antifolate action.

In addition to pemetrexed-induced AKI due to ATN [21], cases of nephrogenic diabetes insipidus (DI) and RTA have also been reported [22]. Patients who have received prior chemotherapy agents that are potential nephrotoxins, and those who have risk factors for CKD such as diabetes or HTN, have a higher risk of kidney injury. Biopsies of kidneys have shown loss of brush borders, tubular atrophy, with some interstitial inflammation [21].

Crizotinib

As the armamentarium of chemotherapeutic agents expands, new drugs are now rapidly entering clinical use. Some of these newer drugs have been reported to cause AKI in a similar pattern to ATN, though their exact mechanisms of toxicity are not often well defined. Crizotinib, a tyrosine kinase inhibitor of multiple pathways including anaplastic lymphoma kinase (ALK), is in increasing use as a therapy for metastatic ALK-positive non-small cell lung cancer. Due to its expedited FDA approval, some of its side effects were not clearly known, and since its release in 2011, several reports of AKI and renal insufficiency have been reported [23–26]. A review of 38 patients who were given crizotinib for an average of 16 months reported a 23.9 % decline in estimated GFR during the initial 12 weeks of therapy. On withdrawal of the drug, the majority of patients recovered kidney function [25]. In one report of an episode of AKI associated with crizotinib, investigators were able to obtain a renal biopsy, which showed ATN as the primary lesion [24], though the mechanism of nephrotoxicity was not defined. In addition to ATN, non-nephrotic range and non-albuminuric proteinuria has also been reported [24].

Carfilzomib

Another example of drug-induced injury is being reported in the treatment of multiple myeloma. Renal disease is not uncommon in multiple myeloma and therefore, a direct causal effect from a single drug is difficult to prove. Nonetheless, there are reports of AKI with carfilzomib, a next generation selective proteasome inhibitor approved for the treatment of relapsed and refractory multiple myeloma. Jhaveri and colleagues reported a case of a patient with IgG kappa multiple myeloma undergoing chemotherapy with carfilzomib and steroids who presented with fever and AKI 9 days after his last treatment, which resolved after conservative management, including drug discontinuation [27]. In a phase 2 trial of carfilzomib in the treatment of multiple myeloma, both acute and chronic renal failure were reported (5 and 3.8 %), and some of these subjects were managed with drug cessation, interruption, or dose reduction [28]. Though the mechanism of renal dysfunction is unknown, some have postulated that N-acetylcysteine may play a protective role in injury prevention, perhaps suggesting a partly prerenal or vasoconstrictive etiology to the AKI [29].

Mammalian Target of Rapamycin (mTOR) inhibitors

Proteinuria is a well-known side effect of mammalian target of rapamycin (mTOR) inhibitors in some patients. However, a new association of mTOR inhibitors with ATN has recently surfaced. Four cases of biopsy-proven ATN occurred in patients undergoing therapy for lymphoma or metastatic malignancy [30]. Two of the cases rapidly recovered after drug discontinuation while the other two remained in renal failure, and one of the cases clearly showed signs of concomitant focal segmental

glomerulosclerosis (FSGS). mTOR activity increases in the kidney after ischemic injury and may be involved in cell growth and repair; mTOR complex 1 (mTORC1), a protein complex formed in part by mTOR kinase, is specifically involved in the upstream inhibition of autophagy [30]. Therefore, induction of autophagy, particularly during times of renal tubular cell stress or injury, may be the mechanism by which these drugs cause renal damage [30]. MTOR inhibitors are used at much higher doses in cancer treatment compared to post-transplant immunosuppression, which may explain the lack of AKI associated with MTOR-inhibitor use in the solid organ transplant population [30].

Clofarabine

Clofarabine is a purine nucleoside analog that exerts its anti-neoplastic effect by inhibiting DNA synthesis and the enzyme ribonucleotide reductase (RNR). It is used routinely for the treatment of relapsed acute lymphoblastic leukemia in children, and it is increasingly also being used for relapsed or refractory acute myeloid leukemia in adults. Two case reports outline patients treated with clofarabine who developed severe renal injury shortly after drug administration; one of the patients was found to have 4 g of proteinuria, and the other was anuric and required dialysis [31, 32]. No biopsy data exist to help propose a mechanism of injury, but RNR inhibition may be contributing to podocyte injury [31].

Androgen Deprivation Therapy (ADT)

Recent epidemiological data has linked androgen deprivation therapy (ADT) to an increased risk of AKI in patients undergoing treatment for prostate cancer. In a group of over 10,000 patients with prostate cancer followed-up for 10 years and matched against selected controls, current ADT was associated with an adjusted odds ratio for hospitalization for AKI of 2.68; this was higher for those who received combined agent versus single agent regimens [33]. Given that ADT is still the mainstay of treatment for advanced prostate cancer, these results will require replication for clinical implications of these data to be confirmed. More population-wide epidemiological studies such as this one may alert us in the future to subtle associations of nephrotoxicity and commonly used chemotherapy agents.

Case #1 Discussion and Follow-Up:
In case #1, both cisplatin and pemetrexed are potential precipitants of AKI. The patient has a higher propensity for AKI due to his baseline CKD. Though volume expansion is important in preventing injury from cisplatin, there is no

evidence to suggest that furosemide or mannitol may be helpful, and mannitol may be detrimental in certain situations. Many newer regimens substitute carboplatin or oxaliplatin for cisplatin, and these are on average less nephrotoxic than the latter. The right answer is b, as the OCT-2 channel transports both cisplatin and ifosfamide into proximal tubular cells, and is critical to their mechanism of injury.

Tubulopathies and Electrolyte Disorders

Case #2
A 47-year-old male and former chewing tobacco user who is diagnosed with surgically unresectable oral squamous cell carcinoma undergoes treatment with docetaxel, cisplatin, and 5-fluorouracil. Follow-up imaging shows progression of disease. Decision is made to start cetuximab monotherapy. After 2 months of therapy, the patient presents with fatigue, weakness, light-headedness, and complains of muscle "twitches." Serum laboratory tests show the following levels: sodium of 129 meq/L, potassium of 3.1 meq/L, chloride of 101 meq/L, HCO3 of 18 meq/L, BUN of 34 mg/dL, and creatinine of 0.9 mg/dL. Glucose is 88 mg/dL, calcium is 7.7 mg/dL, and magnesium is 0.9 mg/dL. His urinary pH is 5.5.

Which of the following is false?

a. His prior cisplatin use likely caused his hyponatremia by potentiation of antidiuretic hormone (ADH) and increased water reabsorption in the collecting duct
b. Both cetuximab and prior cisplatin use could explain his hypomagnesemia
c. His urine should be evaluated for glucose, phosphate, and magnesium
d. His low calcium is likely related to his low magnesium levels

Certain chemotherapy agents impact renal handling of water and electrolytes either by direct cell injury (as described above), or by their effects on specific receptors or channels in distinct segments of the nephron. Due to this some patients develop electrolyte and acid–base derangements as their primary manifestation of renal toxicity. AKI may or may not be present, but regardless of the effect on GFR, the consequences can still be significant and important to recognize.

Proximal Tubule

Injury to the proximal tubule can impede reabsorption of several important electrolytes and compounds, including glucose, phosphate, bicarbonate, and amino acids. The clinical entity that ensues is named FS, and is thus characterized by glucosuria in the absence of hyperglycemia, phosphate wasting, and an RTA due to bicarbonate spilling. Incomplete or partial FS can present with some of these abnormalities but not all.

Ifosfamide is most commonly implicated in inducing FS, and though much of the literature is described in children, a few case reports in adults exist [34]. Even after cessation of therapy, tubular dysfunction from ifosfamide can persist for years, manifesting as partial FS with persistent phosphaturia, as described in childhood malignancy survivors [20]. In adults, this has been reported to lead to osteomalacia [35], and in children may possibly lead to issues with growth and bone development [20]. The doses of ifosfamide associated with FS are variable and not always at the levels associated with AKI or CKD, and the time to onset of symptoms can be immediate or delayed several months. Cisplatin, a proximal tubule cell toxin, is also associated with FS [36], though less commonly than its association with ATN. Imatinib use has also been reported to cause hypophosphatemia from hyperphosphaturia due to a partial proximal tubulopathy [37]. These defects can often go unrecognized and are important to monitor, if undergoing therapy with potential tubular toxins.

Loop of Henle

A principal site of sodium reabsorption, a defect in the loop of Henle can lead to salt wasting and volume depletion (Fig. 4.2, Table 4.1). Cisplatin, in addition to inducing ATN and FS, has been reported to induce a renal salt-wasting syndrome (RSWS) [38]. Affected patients can have profound volume depletion with orthostasis and polyuria, with laboratory tests indicating a hypoosmolar hyponatremia in the setting of a high rate of urinary sodium excretion. With these serum and urine indices, RSWS may be mistaken for syndrome of inappropriate antidiuretic hormone (SIADH) but the key difference between the two is that RSWS has a negative sodium balance despite hypovolemia. A single center report recorded an incidence of cisplatin-induced salt wasting as high as 10 % [39], though in another series a rate of < 1 % was noted [40]. Many of the patients in the former series had sodium wasting for months after discontinuation of cisplatin, and some cases were severe and irreversible [39]. As cases are uncommon, the mechanism is not well characterized at present. Proximal tubular damage likely leads to sodium delivery distally, but in other patients with FS the distal tubules assist in reabsorbing the increased sodium. Loop of Henle dysfunction is therefore postulated, as this is the site of sodium reabsorption that is critical to generating the medullary concentration gradient, which is noted to be impaired in cisplatin toxicity [38]. In support of the loop of Henle being a site of cisplatin injury, magnesium reabsorption occurs via paracellular pathways at the loop of Henle, and hypomagnesemia is reported with cisplatin use [41] (Fig. 4.2).

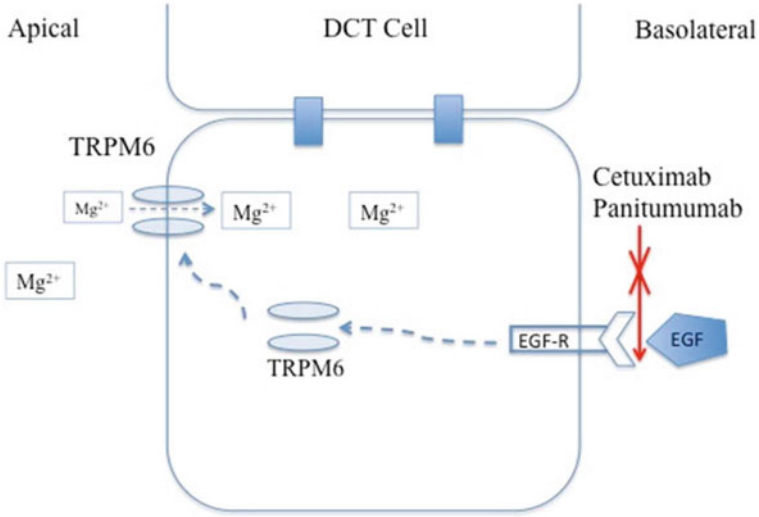

Fig. 4.4 Cetuximab and other EGF-R blockers prevent TRPM6-mediated uptake of distal tubular magnesium reabsorption. *DCT* distal convoluted tubule, *EGF* epidermal growth factor, *TRPM6* transient receptor potential melastatin

Collecting Duct

In addition to sodium, potassium, and water handling, the collecting duct is also responsible for magnesium homeostasis. Maintenance of magnesium stores occurs primarily via the epithelial channel transient receptor potential melastin subtype 6 (TRPM6) on the luminal surface of collecting duct cells. Magnesium reabsorption via TRPM6 has been found to be regulated by epidermal growth factor (EGF) receptor signaling. EGF binds to its receptor on the basolateral surface of the cell; this in turn sets off cellular signaling that facilitates insertion of TRPM6 channels into the apical membrane, thus allowing for magnesium reabsorption (Fig. 4.4) [42]. This interaction is directly antagonized in patients receiving anti-EGFR monoclonal antibodies such as cetuximab or panitumumab therapy, a novel class of chemotherapy agents increasingly associated with renal magnesium wasting.

Cetuximab and panitumumab are used in various epithelial malignancies including head and neck, breast, and lung cancers, but are most commonly employed in the treatment of metastatic or inoperable colorectal cancer. Cetuximab competes for the EGF receptor on epithelial cells, both in malignant and healthy tissue. By binding to the receptor, the antibody inhibits its activation, leading to decreased placement of functional TRPM6 receptors (Fig. 4.4) and magnesium wasting in the urine. Tyrosine kinase inhibitors of the same EGF receptor pathway (e.g., erlotinib) do not appear to induce clinical magnesium wasting with conventional dosing [43].

In a meta-analysis of randomized control trials, cetuximab exhibited an odds ratio of 5.3 versus other agents of inducing significant hypomagnesemia (serum

Mg < 0.9 mg/dL) [44]. In another recent meta-analysis, the relative risk of any hypomagnesemia with panitumumab compared to controls was 12.55 [45]. The overall incidence of hypomagnesemia with anti-EGFR treatment ranges from 10–36 % in clinical trials [46, 47]. Given the direct effect these drugs have on magnesium transport channels, renal magnesium leak with decline in serum levels is common [43]. Cetuximab treatment duration, older age, and higher baseline magnesium levels factor strongly in the risk for development of hypomagnesemia [15]. Furthermore, hypomagnesemia may predict better tumor outcomes [48, 49], though this relationship is yet to be proven definitively. The mainstay of treatment is aggressive magnesium repletion. Oral treatment is commonly limited by gastrointestinal side effects and patient tolerance; intravenous dosing is then required, which is time-consuming and often inadequate. Fortunately, unlike the reabsorption defects seen with cisplatin therapy, magnesium wasting with cetuximab is temporary and eventually resolves 4–6 weeks after discontinuation of the drug [46].

Water handling is also tightly regulated by the collecting duct, and cellular imbalances in reabsorption and excretion at this site can lead to dysnatremias. Certain chemotherapy agents can affect this process. Under normal circumstances, vasopressin is the primary hormone responsible for water reabsorption; it binds to vasopressin receptor 2 (VR2), which initiates a G-protein-coupled signaling cascade that results in the insertion of aquaporin channels in the apical membrane of the collecting duct. These channels are freely permeable to water and when active, allow water to diffuse down its concentration gradient from the tubule into the cell, and then into the systemic circulation. The urine, in turn, becomes concentrated to a degree depending on the amount of vasopressin present.

Cancer patients often have pain or nausea/vomiting, which are potent non-osmotic stimuli for vasopressin release, which can lead to hyponatremia from increased water reabsorption. Cyclophosphamide and vincristine, used commonly in lymphomas and leukemias among other cancers, can potentiate the release and effect of vasopressin, thereby increasing water reabsorption even further [17]. Though cyclophosphamide-induced SIADH has been associated with high-dose IV therapy, several cases linked to low dose IV therapy have been reported, including one case where a single oral dose was felt to lead to hyponatremia after other factors were excluded [50].

Conversely, ifosfamide and cisplatin are both drugs that have the potential to interfere with vasopressin activation of the VR2. This results in nephrogenic DI, where water reabsorption in the collecting duct is impaired and urinary concentration is inhibited. Clinically, patients have symptoms of polyuria and polydipsia, and urine studies demonstrate low specific gravity and osmolarity. Serum sodium levels usually remain in the normal to high-normal range, but if access to water is disrupted, then severe hypernatremia can occur. Fortunately, resolution of nephrogenic DI appears to resolve within days to weeks of drug cessation [51]. Though relatively rare, more cases have been reported with ifosfamide, and more commonly with treatment in children. It also often occurs in concordance with ifosfamide-induced FS [52].

Case #2 Discussion and Follow-Up
In the above case, multiple pathologies come to mind. The patient has significant hypomagnesemia, likely also inducing symptomatic hypocalcemia from ineffective or inadequate PTH activity; he has a non-anion gap metabolic acidosis, associated with hypokalemia, likely due to a proximal RTA; and finally, he also has hyponatremia. Magnesium wasting can certainly be from cetuximab, and may explain all his symptoms, but the magnesium wasting that occurs with cisplatin can also be enduring. A high fractional excretion of magnesium would help confirm renal wasting. His proximal RTA may be explained by his prior cisplatin use and resultant tubular injury leading to FS. To assess this, his urine should be tested for glucose and phosphate. His hyponatremia could be secondary to volume depletion, but could also be caused by cisplatin. Both would present with a high urine osmolarity, but the key to differentiation would be a high urine sodium and urine volume in cisplatin-induced salt wasting (i.e., inappropriate salt loss). Cisplatin is not known to induce hyponatremia by potentiating the effect of ADH.

Renal Vasculature and Endothelial Injury

Case #3
A 53-year-old female is referred to you for proteinuria. Though previously healthy, she has recently been diagnosed with locally resectable colon adenocarcinoma on routine screening and is status post left hemicolectomy with no adjuvant chemotherapy. Follow-up imaging showed an isolated new liver lesion of 4 cm, which is confirmed to be a metastatic disease. She is initiated on oxaliplatin, 5-flourouracil, leucovorin, and bevacizumab in hopes of converting her lesion into a surgically resectable disease, and is currently undergoing her fifth cycle of therapy. A routine dipstick revealed 3 + protein. On examination, her BP was 148/98, and she had 1 + swelling in her lower extremities, with no rash on her skin. Her laboratory tests showcreatinine of 1.2 mg/dL from baseline 1.0 mg/dL prior to chemotherapy. She otherwise feels well.

Which one of the following is a true statement?

a. Her rise in blood pressure is associated with a poor prognosis and her chemotherapy should be discontinued
b. Her proteinuria most likely represents an effect of oxaliplatin-induced renal injury

c. Along with a complete blood count, a haptoglobin, LDH, and reticulocyte count should be checked to rule out hemolysis
d. Her therapy should be discontinued and she should be urgently initiated on plasmapheresis

The relatively new class of medications that target the vascular endothelial growth factor (VEGF) pathway were derived from the insight that malignant cell growth and proliferation is dependent on the ability of tumor cells to promote a high degree of angiogenesis [53]. Interrupting the neoplasm's ability to develop its own vascular supply was a logical objective, and since then numerous agents have been developed that inhibit VEGF signaling at various steps in the process. In the pursuit of antiangiogenesis, however, it has been found that these drugs commonly induce HTN, and in some cases thrombotic microangiopathy (TMA) with AKI, likely due to their effect on the renal vasculature. The mechanism of action of these drugs and the proposed etiology of their adverse renal effects are detailed in another chapter in this book, but we will briefly review common clinical toxicities of VEGF inhibitors .

The most common toxicity associated with these drugs is new or worsened HTN. HTN occurred in 19–24 % of the patients in two reviews of bevacizumab and the TKI, sorafenib [54, 55]. However, with newer therapies, rates may be as high as 87 % [56]. The timing of this effect can vary depending on the host and the agent used, but ambulatory blood pressure monitoring in one cohort showed that 93 % of the patients on sorafenib had a rise in mean arterial pressure in less than a week and blood pressure rose on average by the first day of treatment [57]. In some cases, the HTN associated with anti-VEGF therapy is severe and requires discontinuation of the drug. Cases of reversible posterior leukoencephalopathy syndrome have also been described [58].

Along with HTN, some patients on antiangiogenic treatments also develop proteinuria, microangiopathic hemolytic anemia, thrombocytopenia, and renal failure [59, 60]. These findings are the hallmark of TMA. The exact incidence of this is unclear, as many patients do not develop enough renal insufficiency to warrant a biopsy. However, proteinuria, an early marker for the disease, occurs in 5–13 % of the patients on bevacizumab [54, 61], with 2.2 % having urinary levels greater than 3.5 g per day. In mice, a single dose of systemic anti-VEGF antibody induced a 2–3 times increase in proteinuria, with renal pathology showing findings indicative of TMA [60]. When ablation of VEGF was limited to the podocyte in the same study, TMA was noted, suggesting that local production of VEGF is critical to vascular endothelial integrity [60]. Given this mechanism, the new onset or worsening proteinuria seen in patients on antiangiogenic treatment most likely reflects renal TMA. As such, numerous case reports and case series have documented this lesion on biopsy in treated patients [59, 60, 62].

Gemcitabine, a nucleoside analogue that arrests tumor cell growth by inhibiting DNA synthesis, is used for various solid organ malignancies. Along with the antiangiogenic agents described above, it has also been implicated in AKI due to renal TMA. Though it is rarer than anti-VEGF-induced TMA, occurring in approximately 0.5 % of the patients [63], gemcitabine-associated nephrotoxicity can present similarly with systemic manifestations of hemolysis and thrombocytopenia, along with proteinuria and AKI [64]. Furthermore, gemcitabine-induced TMA can also present with severe skin manifestations, including livedo reticularis [65] and digital necrosis [66]. The mean time to onset of TMA after initiating therapy is around 7.6 months, and HTN and proteinuria are also common [67].

Regardless of the inciting agent, the treatment for chemotherapy-induced TMA is the same at present, and includes supportive care and drug discontinuation when renal insufficiency is severe or progressive. HTN can theoretically contribute to further endothelial injury and dysfunction [68], and should be treated, though specific use of angiotensin-converting enzyme inhibitors (as noted to be beneficial in scleroderma renal crisis, a similar pathology) has not been studied. Steroids, fresh frozen plasma infusion, and plasmapheresis have all been used, but as data from a small nonrandomized study by Izzedine et al. [69] show, none have been proven beneficial. Outcomes vary and some can progress to dialysis-requiring ESRD.

Of note, both anti-VEGF agents and gemcitabine have been associated with other pathological lesions in case reports. Gemcitabine has been reported to cause membranoproliferative glomerulonephritis (MPGN) [70], and FSGS, AIN, and MPGN have all been described with antiangiogenesis drugs [53, 58, 60].

Clinical Case #3 Discussion and Follow-Up
For the patient case, the most likely culprit behind her proteinuria and her HTN is treatment with bevacizumab. A work up to rule out systemic TMA is prudent, and thus the answer is c. Even without systemic manifestations, her proteinuria and HTN may represent TMA limited to the renal vasculature, but with mild renal insufficiency, close monitoring for any worsening should help decide whether or not her therapy should be held or discontinued. Her HTN is not linked to a poor prognosis, and as above, there is no clear role for plasmapheresis in her disease state.

Glomerular Diseases

While TMA often results in proteinuria from vascular damage to the endothelium, proteinuria can also occur from isolated injury to the cells and structures that comprise and reinforce the basement membrane of the glomerulus. If the damage is severe, it can result in full blown nephrotic syndrome (NS) (Table 4.1). Various drugs have been

reported to be secondary causes of NS—IV bisphosphonates such as pamidronate are often implicated—but in the setting of antitumor therapy, interferon (INF) treatment is most closely associated with NS.

IFN is a glycoprotein secreted by leukocytes, fibroblasts, T cells, and natural killer cells, in response to foreign pathogens or tumor cells. It plays an important role in innate immunity and signaling between cells of the immune system. IFN-α and IFN-β act to reduce viral replication and protein synthesis in adjacent cells (when produced by virally infected cells), and IFN-γ stimulates macrophage activation and major histocompatibility complex (MHC) expression [71]. IFN-α is used for chemotherapy in malignancies such as hairy cell leukemia and Kaposi sarcoma, and intravesically in bladder cancer, along with its considerably more common use in the treatment of hepatitis C and B. IFN-β is most commonly used for the treatment of multiple sclerosis. Both have been shown to cause NS [71]. Though the mechanism is not well elucidated, chronic INF therapy appears to injure the podocyte both directly and indirectly. By binding to its endogenous α/β receptor (which is also present on podocytes), IFN directly suppresses cellular proliferation and alters cell metabolism. It also increases the oxidative capacity of macrophages, and increases expression of MHC class II antigens. Indirectly, IFN may activate various adaptive immune mechanisms that result in increased macrophage activation [71]. Interestingly, such a response in macrophages is also seen in hemophagocytic syndrome, which is associated with collapsing FSGS [72]. Furthermore, certain known secondary causes of FSGS, such as viral infections with HIV and parvovirus B10 or SLE, all promote states with high levels of IFN. IFN may also enhance synthesis of various cytokines often cited as putative permeability factors in minimal change disease (MCD) and FSGS [71].

Several cases of MCD, FSGS not otherwise specified, and collapsing FSGS have been described with IFN therapy. Timing of IFN therapy and glomerular toxicity varies widely across patients (from days to years), as does their degree of proteinuria. Based on the limited evidence available, MCD seems to have a good long-term outcome, with remission in nearly all patients [71], but both types of FSGS show only partial remission or none at all, even after discontinuation of IFN therapy [71, 73]. Collapsing FSGS fares more poorly than FSGS not otherwise specified. Though steroids are often used, they do not appear to correlate with remission in FSGS. In the few reported cases of MCD, patients did improve with steroid use but given the high rate of remission, the added utility of steroids is unclear [71, 73]. Though clinical presentation and outcomes are variable, therapy should be discontinued promptly when NS is encountered.

Interstitial Nephritis

Though drugs are the leading cause of AIN, a form of renal injury that is characterized by an inflammatory infiltrate in the renal interstitium, AIN remains an uncommon side effect of chemotherapy agents. Recently, a novel class of monoclonal antibodies that

target cytotoxic T-lymphocyte antigen-4 appear to function as immune modulators of anticancer T cell activity, and have been found to be effective in the treatment of melanoma and several other malignancies. Interestingly, treatment with this class of drugs has been associated with inflammatory disease in various organs, including dermatological reactions, thyroiditis, hepatitis, and enterocolitis [74]. Presumably, these adverse reactions represent T-lymphocyte loss of tolerance to self-antigens due to a direct effect of the drug, rather than an immune response to a drug-specific antigen [75]. A single case report of biopsy-proven AIN has been described; renal pathology showed a dense inflammatory infiltrate, consisting of CD8 + T cells, with no glomerular pathology [75]. Of note, numerous cases of hypophysitis leading to central DI, among other manifestations of hypopituitarism, have been reported in the literature [76]. Regardless of the organ affected, steroids appear to prompt quick resolution in many cases, without evidence of a deleterious effect on antitumor activity [75, 77].

Less commonly, tyrosine kinase inhibitors of the VEGF pathway such as sunitinib and sorafenib have also been reported to cause AIN. The mechanism is unknown, but perhaps due to interruption of certain growth factors that are known to play a role in recovery of renal function after AKI [78].

Crystal Nephropathy

Case #5

A 22-year-old female with left femur osteosarcoma with metastases undergoes treatment with MTX. She is initiated on therapy with pre- and post-hydration with 1/2 normal saline with 75 meq of sodium bicarbonate. Leucovorin rescue is started 24 h later. On day 4 of her hospitalization she develops nausea and vomiting with some epigastric pain. Serum levels of MTX are 41 μmol/L and urine output is noted to decrease to 250 mL over the last 24 h. Laboratory tests show the following levels: sodium of 136 meq/L, potassium of 5.9 meq/L, chloride of 102 meq/L, bicarbonate of 16 meq/L, BUN of 43 mg/dL, and creatinine of 1.9 mg/dL, which is up from a baseline of 1.0 mg/dL.

Which of the following is true?

a. MTX more commonly induces AKI when given in low doses for conditions such as rheumatoid arthritis and psoriasis
b. Both leucovorin and glucarpidase act to reduce serum MTX levels in patients with MTX-induced renal failure
c. A single session of hemodialysis is usually effective in inducing a sustained reduction of MTX levels
d. Further urinary alkalinization may increase the solubility of MTX and its metabolites in her urine

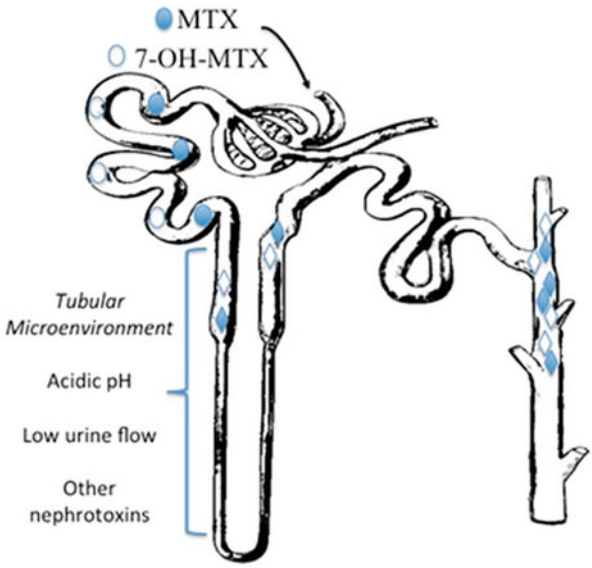

Fig. 4.5 Methotrexate (*MTX*) and 7-hydroxy-methotrexate (*MTX*) are freely filtered across the glomerulus. While they may circulate in their soluble forms (open and filled *circles*), they are prone to form crystal precipitates (open and filled *triangles*) within the microenvironment of the nephron, particularly in the distal tubule

In the urinary tract itself, from the developing tubules of the renal parenchyma leading to the urethra, certain drugs and their metabolites can precipitate and form crystalline particles in the urine. Occasionally this deposition of crystals within the tubular lumen can lead to crystal nephropathy or crystal-induced AKI. Deposition and injury depend on various urinary and host factors, including urine pH, baseline renal function, and volume status [79]. In the treatment of cancer patients, this type of drug-specific injury is seen most commonly with the use of MTX .

MTX is an antimetabolite commonly used in the treatment of a variety of malignancies, ranging from acute lymphoblastic leukemia and lymphoma to solid tumors such as osteosarcoma and breast cancer. It is also used in the treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis, and less commonly in systemic lupus erythematosus. Due to this, daily doses range anywhere from 20 mg/m^2 (in RA or psoriasis) to intravenous doses as high as 1000–33000 mg/m^2 [2]. This high dose IV therapy (HDMTX) is used in anticancer regimens, and is associated with crystal-induced AKI.

MTX works by competitively inhibiting the enzyme dihydrofolate reductase (DHFR) by binding at the folate binding site (Fig. 4.3). DHFR is responsible for converting dihydrofolate to tetrahydrofolate, which is a principal building block in the synthesis of purine and pyrimidines. Thus, the use of MTX blocks RNA and DNA synthesis, and in turn inhibits the rapid cell division which characterizes tumor cells. High doses are given as an IV infusion, and leucovorin (i.e., folinic acid, which converts dihydrofolate into tetrahydrofolate independent of DHFR) is given 24–36 h after the drug to prevent nonmalignant cell injury while maximizing tumor cytotoxicity [17, 79].

The principal mechanism of AKI induced by MTX is not clearly known, but felt to be due to crystal precipitation in distal tubules (Fig. 4.5), although some direct tubular

injury may also play a role via oxygen radicals and decreased adenosine deaminase activity [80]. MTX and its major metabolites, 7-OH MTX and 2,4-diamino-N10-methylpteoroic acid, are filtered by the glomerulus and secreted into the proximal tubule [15]. These two primary derivatives of the parent drug are six- and tenfold less soluble in urine than MTX, respectively [81]. When MTX is given with leucovorin rescue at the abovementioned doses and with proper preventive strategies, AKI occurs in 1.8 % of patients in trials of osteosarcoma patients [82]. Mortality in those that exhibited AKI was 4.4 % [82]. As 90 % of MTX is cleared by the kidneys, severe and prolonged AKI can result in markedly decreased excretion, higher serum levels, decreased effectiveness of leucovorin rescue, and subsequently an increased risk for other known systemic toxicities of MTX, such as bone marrow suppression, neurotoxicity, hepatitis, and mucositis.

Prevention of MTX toxicity and AKI is achieved by aggressive volume repletion to maintain high urinary flow rates. This allows for excretion of the drug and decreased tubular precipitation. Since MTX crystal formation occurs in acidic environments, alkaline fluid is used to raise the urinary pH. An increase in pH from 6.0 to 7.0 results in a five- to eightfold increase in the solubility of MTX and its metabolites [2]. Leucovorin, as discussed above, is used as a rescue to avoid systemic toxicity, but does not act to decrease serum MTX levels. Hemodialysis has been used when AKI is prolonged, with high flux membranes deemed most potent in achieving serum level reduction [83, 84]. However, since the majority of MTX is intracellular, levels tend to rebound quickly after dialysis cessation, and continuous modalities of dialysis or repeated sessions are often required. Carboxypeptidase G2 (glucarpidase) is a relatively new recombinant enzyme that metabolizes MTX into nontoxic derivatives. In a retrospective trial of 100 patients with high serum levels and MTX-induced nephrotoxicity, glucarpidase lowered levels by 98 % within 15 min [85], and most subjects did not require any additional dosing. Practically, glucarpidase results in metabolites of MTX that can cross-react with commercial MTX assays, so interpretation of serum levels post-dosing can be problematic. Furthermore, leucovorin is metabolized by glucarpidase as well, and should not be dosed within 2 h of the enzyme being dosed. While there is still a lack of randomized controlled evidence proving its efficacy over current conventional management for MTX removal and availability may be an issue, glucarpidase may ultimately be an advantage over high flux hemodialysis since rebound in serum drug levels is not seen.

Case #5 Follow-Up and Discussion

In our patient above, the answer to the question is d. Her renal failure is likely due to MTX toxicity, as her levels are still high several days after her infusion, and she is becoming oliguric with significant renal dysfunction. This most commonly occurs with high dose IV therapy. Though difficult with concomitant oliguric renal failure, increasing the alkali in her IV fluids may help promote urinary solubility of MTX and its metabolites if her urine is acidic. Dialysis may be required, though a single session is unlikely to be effective.

Leucovorin will not lower her drug levels, but if the cost is not prohibitive and availability is not an issue, glucarpidase will likely rapidly reduce her MTX burden and could be considered an alternative to initiating dialysis.

Chronic Kidney Disease (CKD)

All drugs that induce AKI carry the risk of irreversible damage and long-term CKD. However, a few notable chemotherapeutic drugs appear to carry a risk of renal insufficiency over the long-term without a high propensity for episodes of AKI.

The nitrosoureas are a group of alkylating agents that can cross the blood–brain barrier and are used for certain CNS malignancies and increasingly in other cancers as well. They are associated with a dose-dependent renal injury that is characterized by indolent and slowly progressive CKD over a period of months to years. Biopsy studies are characterized by tubular atrophy, interstitial fibrosis, and glomerulosclerosis [86]. Streptozocin is associated with AKI as well, via production of an N-nitroso metabolite which is not found on carmustine or lomustine [87]. A recent case report of carmustine and etoposide causing AKI in a bone marrow transplant recipient also was reported [88]. However, chronic scarring and fibrosis are the more common lesions, and semustine and streptozocin appear to carry a higher long-term risk for CKD than carmustine and lomustine [89]. The etiology of this insidious renal injury is not yet understood.

As previously discussed, ifosfamide is associated with tubulopathies and also AKI. However, exposure also has been shown to cause long-term renal insufficiency. A 22 ml/min reduction in GFR was found over 5 years in an adult cohort treated with ifosfamide [90]. In childhood cancer survivors followed for a median of 21 years, ifosfamide was associated with a long-term decline in GFR when compared to patients given other chemotherapy medications, though cisplatin was also associated with some risk of CKD [91]. CKD, in addition to the phosphaturia and other electrolyte abnormalities associated with ifosfamide-induced tubular dysfunction, can be chronic, and in children lead to growth problems and in the elderly to osteomalacia.

Summary

Chemotherapy is life-prolonging and life-saving therapy for patients with malignant diseases. However, higher concentrations despite having higher potential antitumor activity can prove to be deleterious to healthy tissues, including kidneys. Various patterns of nephrotoxicity may result, leading to AKI or CKD or causing isolated

proteinuria or electrolyte disturbances. Early recognition of chemotherapy associated nephrotoxicity and interventions such as dose reduction, effective plasma volume restoration, and elimination of concomitant nephrotoxic agents and events are essential to prevent and attenuate kidney injury and improve patient outcomes.

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Chapter 5
Biological Cancer Therapies and the Kidney

Benjamin D. Humphreys

List of Abbreviations

ABPM	Ambulatory blood pressure monitor
AKI	Acute kidney injury
CKD	Chronic kidney disease
CML	Chronic myelogenous leukemia
EC	Endothelial cells
EGFR	Epidermal growth factor receptor
eNOS	Endothelial nitric oxide synthase
ET	Endothelin
GFR	Glomerular filtration rate
GIST	Gastrointestinal stromal tumor
NO	Nitric oxide
TKI	Tyrosine kinase inhibitors
TMA	Thrombotic microangiopathy
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

The idea of targeted therapies to treat cancer can be traced back to the original hypothesis, proposed by Dr. Judah Folkman in 1971, that tumor growth and metastases are angiogenesis-dependent processes [1]. This hypothesis proposed that tumor cells communicate with vascular endothelial cells (EC) within developing neoplasms via diffusible growth factors, leading to increased vascularization, which further facilitates tumor growth. Interrupting pro-angiogenic biologic signaling pathways is the primary objective of antiangiogenic strategies, and this class of drugs is growing rapidly in the treatment of solid tumors.

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Table 5.1 FDA-approved biologic therapies and kidney toxicities

Class	Examples	Kidney toxicity
Antiangiogenic therapy	Bevacizumab, sunitinib, sorafenib, pazopanib, everolimus	Hypertension, proteinuria, TMA, AKI
EGFR inhibitors	Cetuximab, erlotinib, gefitinib, lapatinib, panitumumab	Hypomagnesemia, hypokalemia
Multifunctional TKIs	Imatinib, dasatinib, ponatinib, bosutinib	AKI, CKD, proteinuria, TMA

AKI acute kidney injury, *CKD* chronic kidney disease, *TMA* thrombotic microangiopathy

Targeted therapies now cover a range of new signaling cascades. Two other examples include the epidermal growth factor receptor (EGFR) pathway and multi-targeted tyrosine kinase inhibitors (TKI) such as imatinib. In each case, drugs are targeted on specific cancers that rely on a specific signaling pathway for survival and expansion. Because these drugs are both specific and highly potent, toxicities are now a well-recognized consequence of these therapies. Typically, these toxicities result from inhibition of the biologic pathway in a non-cancer tissue, where the pathway regulates some aspect of organ homeostasis. The EGFR regulates magnesium handling in the kidney, for example, and hypomagnesemia is a prominent side effect of EGFR inhibitors.

Nephrologists need to be aware of the presentation, prevention, and treatment of toxicities associated with targeted therapies [2, 3]. Risk factors for toxicity include increasing patient age, exposure to other nephrotoxins, preexisting chronic kidney disease (CDK), and volume depletion. Kidney toxicities are often cumulative, and high dose or prolonged therapy increases the risk of renal dysfunction. Whereas acute kidney injury (AKI) generally improves when diagnosed early, there is a very real risk of permanent CKD due to chemotherapy. In patients being actively treated for cancer, CKD often limits their eligibility for other therapies and clinical trials, emphasizing the importance of prompt recognition and treatment. This chapter reviews the kidney toxicities of antiangiogenic therapies, of EGFR inhibitors, and of other multi-targeted TKIs. Table 5.1 presents an overview of Food and Drug Administration (FDA)-approved biologic therapies and associated kidney toxicities.

Case #1

A 58-year-old woman is referred to you for evaluation and management of hypertension. She was diagnosed with metastatic ovarian cancer 3 years ago and underwent de-bulking surgery followed by taxol and carboplatin. She recently progressed, and was started on bevacizumab monotherapy 4 months ago. She had a history of hypertension for 10 years, controlled with atenolol 100 mg per day. Since starting bevacizumab, she has experienced exacerbated hypertension, with values of 175/105 mm Hg, necessitating the addition of lisinopril 10 mg per day. However, she remains hypertensive (160/95 mm Hg) and is referred for further evaluation.

Although she complains of fatigue, she has tolerated the bevacizumab well, without headache, visual changes, or ankle swelling. Her exam is notable for a blood pressure (BP) of 158/97 mm Hg, normal fundoscopic exam, and no edema. Laboratories shows serum creatinine (1.0 mg/dL), hemoglobin (13.8 g/dL), and platelets (337,000 per/dL). Her haptoglobin is normal and there are no schistocytes on the smear. There is 1 + protein on the dipstick, and the sediment is bland. Urine protein to creatinine ratio is 0.6 g/g creatinine.

What is the mechanism of hypertension related to bevacizumab or other anti-vascular endothelial growth factor (VEGF) therapy (more than one possible answer)?

a. Elevated renin production due to VEGF inhibition
b. Reduced vasodilatory nitric oxide (NO) produced as a consequence of inhibition of the intrinsic tyrosine kinase activity of VEGFR2 that normally couples with endothelial nitric oxide synthase (eNOS)
c. Microcapillary rarefaction
d. Endothelin-1 (ET-1)-induced hypertension

Antiangiogenic Therapies

Antiangiogenic therapies target the VEGF molecule, its receptor, or downstream pathways. FDA-approved antiangiogenic agents include bevacizumab, a recombinant humanized monoclonal antibody that binds and sequesters the VEGF molecule, [4] and multi-targeted TKIs, small molecules that inhibit the vascular endothelial growth factor receptor (VEGFR) intracellular intrinsic kinase activity, such as sunitinib, sorafenib, axitinib, and pazopanib [5]. TKIs are not entirely specific for VEGFR2, they also have inhibitory activity against other receptor tyrosine kinases, such as the platelet-derived growth factor receptor or c-Kit. The use of these medications has since expanded to many different solid tumors, with numerous clinical trials of newer formulations of the medications underway. Antiangiogenic therapies are now the first-line therapies for cancers such as metastatic renal cell carcinoma, which accounts for 2.5 % of all new cancer diagnoses. With increased use of these medications and many highly potent formulations in development, there is an increasing clinical need to understand how to diagnose and manage VEGF inhibitor toxicities.

Hypertension Caused by Antiangiogenic Therapies

Hypertension is a very common toxicity of antiangiogenic therapy. Hypertension occurs in 19–24 % of patients receiving FDA-approved therapies [6, 7], but it can occur in up to 80 % of patients on the newer experimental forms of these medications [8].

Nearly all patients taking these drugs experience a rise in BP, even if not to hypertensive levels. With high-potency TKIs, BP rise can be rapid—within days. On the other hand, with biologic therapies such as bevacizumab, the rise can be slower, over weeks or months, as in the patient in Case #1. In one study examining sorafenib, among 54 patients initiating therapy, 93 % had a rise in BP by day 6, and most experienced a rise in BP over the first 24 h of therapy, as assessed by ambulatory blood pressure monitoring (ABPM) [9, 10]. BP typically falls when treatment is interrupted. We reported a very rapid rise in BP among women initiating cediranib therapy, a high-potency small-molecule VEGF-targeted therapy, with 67 % of patients developing hypertension over the first 3 days of therapy, and 87 % by the end of the study [8].

The binding of VEGF to its receptor VEGFR2 activates the intrinsic tyrosine kinase activity of VEGFR2, which couples with eNOS and increases synthesis of vasodilatory NO [11]. Based on this, inhibition of VEGF signaling decreases NO bioavailability, causing vasoconstriction. Indeed, VEGF inhibition is associated with decreased urinary nitrite/nitrate excretion and decreased serum levels of NO metabolites in humans [12, 13], although no difference in flow-mediated dilation, a surrogate for NO bioavailability, has also been reported [13]. Treating mice with an anti-VEGFR2 antibody causes a rise in BP and reduces kidney eNOS and nNOS [14]. On the other hand, in a swine model of sunitinib-induced hypertension, NO bioavailability does not appear to contribute to sunitinib-induced hypertension [15]. Despite some conflicting evidence in the literature, most evidence to date does implicate increased peripheral vascular resistance in the pathophysiology of antiangiogenic therapy-induced hypertension.

Another important factor underlying antiangiogenic therapy-induced hypertension is ET-1, a potent vasoconstrictor. Sunitinib induces a rise in circulating levels of ET-1 in rodents, as well as in humans [16]. ET-1 levels rise rapidly after starting regorafenib, a TKI, and they normalize just as rapidly after discontinuation [17]. Pig models suggest that the rise in BP induced by antiangiogenic therapy can be prevented ET receptor antagonists [15, 18]. Since antiangiogenic therapies induce generalized endothelial dysfunction, which itself is a known trigger of ET-1 secretion [19], it is likely that this also plays a role in the underlying pathophysiology.

A third factor in antiangiogenic therapy-induced hypertension is microcapillary rarefaction. Although the data supporting a role for this are less strong, several observations suggest it may be playing a role. Rodents treated with VEGF inhibitors experience regression of tracheal capillary networks by up to 30 % at 21 days of therapy, and this process reverses with antiangiogenic therapy discontinuation [20]. In humans, capillary density reduction has been measured in patients taking either bevacizumab or TKIs, of the order of 10–20 % reduction [21, 22]. It is important to note, however, that increasing peripheral vascular resistance by 5 % requires rarefaction of 40 % of the microcapillary bed—more than what has been observed in humans [16, 23]. At the present time, more research is needed to better define the role of capillary rarefaction in antiangiogenic therapy-induced hypertension.

Other pathways may also be playing roles. A shift in the pressure–natriuresis curve, causing volume overload, has been reported by Facemire and colleagues [14]. Macrophage-derived VEGF-C has been proposed to regulate lymphangiogenesis and

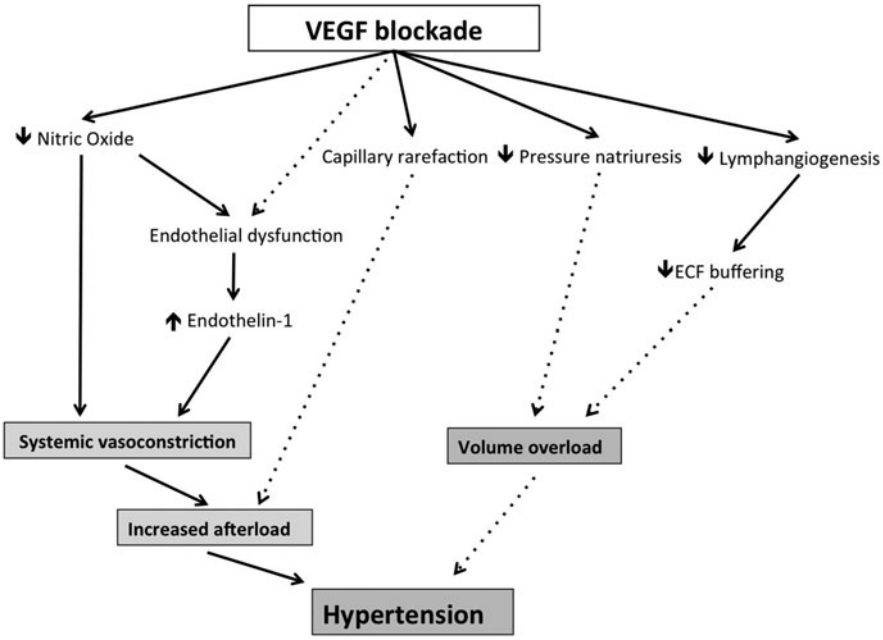

Fig. 5.1 Multiple mechanisms by which VEGF blockade induces hypertension. VEGF signaling blockade inhibits NO production, enhances endothelin-1 secretion, and causes capillary rarefaction. All of these effects cause increased afterload and consequent increased blood pressure. In addition, VEGF blockade shifts the pressure–natriuresis curve, and decreases lymphangiogenesis and both of these effects contribute to volume overload and hypertension

extracellular fluid buffering, and anti-VEGF therapies may interrupt this capacity [24]. The degree to which these pathways and others, such as prostaglandins or reactive oxygen species might contribute remains unclear [25]. Figure 5.1 summarizes these pathways.

Case #1 Follow Up and Discussion
Choices b, c, and d are correct. Reduced vasodilatory NO produced as a consequence of inhibition of the intrinsic tyrosine kinase activity of VEGFR2, which normally couples with eNOS, microcapillary rarefaction, and ET-1-related effects are important mechanisms. Renin is not a major described mechanism in these agents.

Case #2
A 78-year-old woman with renal cell carcinoma is referred to you for proteinuria. She has a history of hypertension controlled with hydrochlorothiazide and diabetes on metformin. She started sunitinib 11 months ago, and had no proteinuria by urinalysis at that time. She developed ankle edema 5 months ago, and a 24-h urine collection was performed that showed 7.2 g of proteinuria. Her hydrochlorothiazide dose was increased. Last month her edema worsened, and she was referred to you.

She complains of significant ankle swelling. Her exam is notable for a BP of 152/93 mm Hg and 2+ pitting edema to her mid-thighs bilaterally. Serum creatinine is 1.4 mg/dl and her urine protein to creatinine ratio is 10.9 g/g creatinine. Urinalysis shows 1+ hematuria with 3+ protein. What is the most likely mechanism of her proteinuria?

a. Minimal change disease
b. Membranous nephropathy
c. Hyperfiltration-related focal and segmental glomerulosclerosis
d. Thrombotic microangiopathy (TMA)

Proteinuria After Antiangiogenic Therapies

Proteinuria after antiangiogenic therapy is most commonly the consequence of renal TMA.

Case #2 Follow-Up and Discussion
Proteinuria on the administration of antiangiogenic therapy is most commonly the consequence of renal TMA. The clinical syndrome is characterized by hypertension, microangiopathic hemolysis, renal failure, sub-nephrotic proteinuria, and microscopic hematuria. Complement levels are typically normal. Haptoglobin levels may be low, and schistocytes can be present on smear, reflecting renal-limited microangiopathic hemolysis. On renal biopsy, endotheliosis is the most prominent feature, and endothelial injury is reflected by thickened basement membranes with double contours. Answer d is correct.

In one study of 1850 patients receiving bevacizumab, the incidence of new proteinuria ascribable to bevacizumab was about 5–10 % and the risk was dose-dependent (RR, 1.4 with low-dose bevacizumab; 95 % confidence interval, 1.1–1.7; RR, 2.2 with high dose; 95 % CI, 1.6–2.9) [6]. This proteinuria probably reflects renal TMA. In a larger meta-analysis (12,268 patients), the incidence of any grade proteinuria associated

with bevacizumab was found to be 13.3 % (95 % confidence interval, 7.7–22.1 %) [26]. The incidence of high-grade proteinuria (greater than 3.5 g per day) was 2.2 % (95 % CI 1.2–4.3 %), and the incidence of nephrotic syndrome was 0.8 % (95 % CI 0.4–1.8 %) with a relative risk of 7.78 (95 % CI: 1.80–33.62; $P = 0.006$).

The kidney histology in patients who develop proteinuria after starting antiangiogenic therapy includes endotheliosis, focal foot process effacement, evidence of glomerular basement membrane damage, including double contours and mesangiolysis. In severe cases fibrin deposition and red blood cell entrapment is also seen. These are the histologic characteristics of renal TMA.

The pathophysiology of this syndrome involves VEGF expressed by podocytes and implicates podocyte–EC crosstalk [27]. Eremina et al. investigated the role of podocyte-derived VEGF in the maintenance of the glomerular filtration barrier. Using conditional mouse genetic models, they specifically ablated VEGF from podocytes alone, and showed that this was sufficient to cause renal TMA [28]. Thus, antiangiogenic therapies act by blocking the effect of podocyte-derived VEGF on adjacent glomerular EC, resulting in disruption of the glomerular filtration barrier with proteinuria, as well as enhanced clotting [29]. Numerous reports have now documented that renal TMA lesions are the most common pattern of glomerular injury found in humans receiving antiangiogenic therapy [28, 30–33]. However, other biopsy findings have also been reported, including immune complex glomerulonephritis [31, 34, 35] and allergic interstitial nephritis [36–38].

Case #3

You are referred a patient for evaluation of hypomagnesemia on cetuximab therapy. The patient is a 59-year-old male with metastatic colon cancer previously treated with the FOLFOX regimen. He had progression and was changed to cetuximab infusions weekly. Electrolytes and renal function were all normal at the start of the therapy. Four weeks later the patient complained of generalized fatigue and muscle weakness. Chemistries revealed a potassium level of 3.2 mg/dL and magnesium of 0.9 mg/dL. You order a fractional excretion of magnesium, which revealed high urinary magnesium levels despite low circulating magnesium. He received IV repletion and was started on oral magnesium oxide, titrated up to maintain magnesium level higher than 1.2 mg/dL; despite high oral magnesium doses his magnesium levels do not normalize while on cetuximab, however.

What are the risk factors for the development of hypomagnesemia with cetuximab therapy?

a. Duration of therapy
b. Race (African Americans)
c. Elderly
d. CKD

Toxicities Associated with EGFR Inhibition

Inhibition of the EGFR is a recognized cause of both hypomagnesemia and secondary hypokalemia. Monoclonal antibody inhibitors of the EGFR include cetuximab and panitumumab. Small-molecule EGFR inhibitors include gefitinib and erlotinib. The overall incidence of hypomagnesemia in patients treated with these drugs is 17 %. Compared to controls not receiving anti-EGFR therapy, the relative risk of hypomagnesemia for cetuximab was 3.87, and the relative risk for panitumumab was 12.55 [39]. Because renal magnesium handling is dependent on normal EGFR signaling, hypomagnesemia reflects adequate EGFR inhibition in vivo and may therefore serve as a surrogate of anticancer efficacy. Indeed, early hypomagnesemia could be a biomarker for superior cancer response. In a study of KRAS wild-type colorectal cancer patients, those that developed an early fall in magnesium > 50 % by day 28 had a higher tumor response rate (55.8 vs. 16.7 %, $P < 0.0001$) and a longer overall survival (11.0 vs. 8.1 months, $P = 0.002$) [40].

The mechanism by which EGFR regulates renal magnesium handling has been characterized. Magnesium reabsorption occurs in the distal convoluted tubule. EGF binds its receptor, EGFR, on the basolateral membrane of distal tubule epithelial cells [2]. EGFR-dependent signals induce translocation of the transient receptor potential M6 (TRPM6) channel, which mediates magnesium reabsorption into the apical membrane. Anti-EGFR antibodies prevent epidermal growth factor (EGF) from binding to EGFR, and thereby reduce TRPM6 insertion into the membrane, inducing renal magnesium loss and hypomagnesemia. Interestingly, this effect is much more pronounced with anti-EGFR antibodies compared to small-molecule receptor inhibitors [41].

Case #3 Follow-Up and Discussion
The primary risk factor for development of EGFR-inhibitor associated hypomagnesemia is duration of therapy, with elderly patients also at higher risk [42]. Choices a and c are correct.

Magnesium levels should be monitored every 2–4 weeks, with special attention paid to levels in elderly patients. Repletion of moderate to severe hypomagnesemia is challenging. Oral magnesium preparations such as magnesium oxide are limited by diarrhea, which exacerbates magnesium losses. Intravenous repletion is limited by the duration of infusion, and the fact that magnesium levels typically fall to previous levels within 3–4 days [43]. In severe cases, intravenous repletion may be required twice weekly. Hypomagnesemia is reversible with discontinuation of anti-EGFR therapy, usually normalizing within 4–6 weeks.

Other TKI Renal Toxicities

TKIs have revolutionized the therapy of chronic myelogenous leukemia (CML) and gastroinstestinal stromal tumor (GIST). First approved in 2001, imatinib is the prototype targeted therapy designed to inhibit the c-Abl kinase, which is activated in both CML and GIST. Now, the second generation TKIs have been developed, including dasatinib, nilotinib, bosutinib, and ponatinib. These agents generally possess increased potency and differing TKI inhibitory profiles. Although these agents have an excellent long-term safety record, very recent evidence suggests that there are kidney toxicities associated with this drug class.

Two recent reports suggest an increased risk of both AKI and CKD with long-term use of imatinib. Marcolino and colleagues analyzed 105 CML patients treated with imatinib for a median of 4.5 years (interquartile range, 3.2–6.1 years). Over this time, 7 % of patients developed AKI (Cr rise of ≥ 0.3 mg/dL or ≥ 50 % increase). More impressively, 16 % developed new CKD, defined as eGFR ≤ 60 ml/min/m^2. Due to the small size of this study, risk factors for AKI and CKD could not be determined, but the authors concluded that imatinib therapy predisposed to loss of GFR [44]. In a very recent study, Yilmaz et al. reported on 475 patients treated with either imatinib, dasatinib, or nilotinib. Of the 442 patients that did not have CKD at the start of therapy, 11 % developed new CKD over a median follow-up of 50 months [45]. These two studies point to previously unappreciated toxicities of TKIs. Their mechanism remains undefined and more studies are clearly needed, particularly since indications for TKIs are broadening.

There are also several case reports describing renal dysfunction, including proteinuria, on TKIs. One Phase 1 clinical trial of dasatinib reported proteinuria in 18 % of patients [46]. In a recent case report dasatinib was associated with the development of nephrotic-range proteinuria, and biopsy revealed a TMA pattern of injury [47]. Several cases of AKI have also been reported with dasatinib [48, 49]. As the clinical experience with newer TKIs develops, it will be important to define the renal risks with these new and effective cancer therapies.

With the increasing use of targeted therapies to treat cancer, the list of targeted therapy-induced kidney toxicities will grow in the future. Nephrologists will be required to recognize and treat these toxicities to optimize outcomes.

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Chapter 6
Rational Dosing of Chemotherapy in Patients with Kidney Failure

Ali J. Olyaei, Edgar V. Lerma, Sascha A. Tuchman and Matthew A. Sparks

List of Abbreviations

AA	African American
ABW	Adjusted body weight
ATP	Adenosine tri-phosphate
AUC	Area under curve
CG	Cockroft–Gault
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CPY	Cytochrome P450 class
CrCL	Creatinine clearance
CT	Computed tomography
EKSD	End-stage kidney disease
GFR	Glomerular filtration rate
GI	Gastro intestinal
HD	Hemodialysis

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Hgt	Height
IBW	Ideal body weight
PD	Peritoneal dialysis
PET	Positron emission tomography
PPI	Proton pump inhibitor
MDRD	Modified diet in renal disease
MW	Molecular weight
Vd	Volume of distribution
Wgt	Weight

Safe and effective administration of chemotherapy is essential to fully realize the anticancer potential of these agents. However, unique challenges arise in patients with diminished kidney function such as patients with chronic kidney disease (CKD) of varying degrees—from stage I CKD to end-stage kidney disease (ESKD). Effective medication management in patients diagnosed with malignancy can be significantly influenced by the physiologic state of the patient. For example, the presence of volume depletion at the time of chemotherapy administration can have profound consequences. The nature of the underlying kidney disease, and the degree of preexisting CKD when cancer is diagnosed, or the development of CKD from chemotherapy agents used in the previous cycles of cancer treatment alter the drug elimination/metabolism process. Compounding the problem is the fact that this population is frequently maintained on multiple medications, thereby potentially creating adverse effects from multiple drug interactions. Special attention is needed in treating patients with malignancy and CKD in order to prevent drugs from reaching toxic levels, and thereby causing further harm to already vulnerable patients. Estimating kidney function and adjusting drug dosages accordingly are important precautionary steps in reducing side effects and successfully treating the underlying malignancy [1, 2].

Appropriate drug dosing is paramount to the successful management of oncological diseases and alterations in drug distribution within the body may influence pharmacologic effects of most drugs. Achieving a therapeutic level depends upon several factors, namely: dose and route of drug administration, bioavailability, and how extensively and rapidly the body metabolizes or excretes these agents. Both oncologists and nephrologists face a major challenge in balancing these factors and need to have an in-depth understanding of the processes of pharmacodynamics and pharmacokinetics. Pharmacodynamics is the study of the effects of drugs on the body [3, 4]. Drugs interact at the site of action with either receptors on cell membranes, enzyme complexes, cellular proteins, or nucleic acids. As such, drugs can have effects that can range from just a few minutes to as long as several hours to days, depending on the site of action and other factors [5]. Pharmacokinetics, on the other hand, is the study and analysis of the time course and distribution of the drug in the body [4]. Pharmacokinetics defines how chemotherapeutic agents are absorbed, distributed, and eventually eliminated from the body. In patients with CKD and malignancy, one must attempt to choose chemotherapeutic agents that are eliminated primarily by hepatic metabolism or cleared/inactivated enzymatically. If this is not

possible, and a chemotherapeutic agent is selected with predominant kidney clearance, then appropriate dosing based on a patient's creatinine clearance is required. The prescribing clinician should also try to avoid any other concurrent drugs with inherent nephrotoxicity [6].

This chapter starts with three cases to illustrate drug management concerns with chemotherapy in CKD patients. Following that, there will be a detailed discussion on drug absorption, drug distribution, metabolism, renal clearance, and dose adjustments.

Case #1

A 70-year-old man with a history of Crohn's disease in remission after prior therapy with infliximab presented to his local physician with generalized weakness of several months' duration. A workup demonstrated anemia, reduced kidney function (serum creatinine 2.2 mg/dL, CrCl, Cockcroft Gault of ~ 28 ml/min) and a large IgG-lambda monoclonal gammopathy on serum protein electrophoresis. A bone marrow aspirate and biopsy demonstrated 80 % abnormal plasma cells and stains were negative for amyloid deposition. During his workup, he rapidly became hypercalcemic (12.5 mg/dL) and his kidney function continued to decline, prompting hospitalization, and initiation of hemodialysis for uremia and hyperkalemia, as well as treatment with pamidronate for hypercalcemia. Myeloma cast nephropathy and kidney injury from hypercalcemia was presumed given the nature of his disease. Although therapy with the immunomodulatory agent lenalidomide was discussed, lenalidomide is cleared by the kidney. He was initiated on chemotherapy with twice-weekly subcutaneous bortezomib, with weekly, oral cyclophosphamide, and dexamethasone—a highly active regimen in myeloma that does not require any adjustment for decreased kidney function. He achieved a complete response (i.e., complete disappearance of monoclonal gammopathy from serum and urine, as well as reduction in bone marrow plasmacytosis to <5%)) and came off dialysis after approximately 6 months. His CrCl returned to normal (94 ml/min, Cockcroft Gault).

The patient recalled reading about the use of lenalidomide in the treatment of his disease. What do you advise this patient?

a. Lenalidomide is ineffective in the treatment of his disease.
b. Lenalidomide is less effective than bortezomib in the treatment of his disease.
c. Lenalidomide has been shown to improve kidney function in some patients.
d. Lenalidomide is absolutely contraindicated in patients with decreased kidney function.

Case #1 Follow up and Discussion: Correct Answer: c

This case illustrates the issues surrounding how diminished kidney function is taken into account when using commonly used chemotherapeutic agents and the importance of rapid initiation of anticancer therapy for presumed cases of paraprotein-mediated kidney injury. Given the potential for recovery of kidney function in these diseases, drug dosing becomes extremely important [7]. Over the past 10 years, four agents have been approved by the US FDA for treatment of multiple myeloma, namely: bortezomib (a proteosome inhibitor), lenalidomide and thalidomide (both immunomodulatory agents), and doxorubicin (a liposomal agent). As such, debates exists about the accepted standard treatment of relapsed/refractory multiple myeloma. Experts recommend that salvage therapy needs to be based on individual clinical profiles, with the risks and potential effects of treatment-related adverse events being the major determinants. Lenalidomide combined with dexamethasone is known to be an effective and well-tolerated regimen for relapsed/refractory multiple myeloma. Furthermore, this combination has shown to be effective and well tolerated in patients with moderate or severe renal dysfunction [8, 9] albeit with an increase in myelosuppression. Secondary to lenalidomide's predominant renal route of excretion the plasma concentration and half-life of the drug are significantly increased in patients with diminished kidney function. Therefore, current recommendations include lowering the starting dose to avoid toxicity and increased risk of adverse events, while still maintaining a therapeutic index. A few studies [9, 10] have demonstrated that the use of lenalidomide was even followed by an improvement in kidney function after treatment. Interestingly, one study [11] compared three regimens; lenalidomide/dexamethasone (RD) versus cyclophosphamide/lenalidomide/dexamethasone (CRD) versus cyclophosphamide/bortezomib/dexamethasone (CyBorD) in newly diagnosed multiple myeloma. These authors concluded that the CyBorD regimen demonstrated superior responses and less frequent serious toxicity but more neuropathy when compared to RD and CRD. More importantly, 80 % of patients treated with modern therapeutic approaches were alive at 4 years

Case #2

A 62-year-old woman presented with a lung mass found on a chest X-ray performed for cough. Chest computed tomography (CT) performed without contrast demonstrated a 3 cm invasive mass with hilar lymphadenopathy. Bronchoscopy was consistent with poorly differentiated squamous cell carcinoma (non-small cell lung cancer). Positron emission tomography (PET)/CT was consistent with resectable disease and so she underwent surgical resection.

Pathological staging (stage IIB) indicated a high risk of recurrence and that the patient would likely benefit from adjuvant (postoperative) cisplatin-based chemotherapy, which is standard of care. However, she also had a baseline CrCl of 32 ml/min (Cockcroft Gault) due to a long history of poorly controlled type 2 diabetes and hypertension.

What adjuvant chemotherapy should be employed in this patient?

a. Full dose cisplatin
b. 50 % reduced dose of cisplatin
c. Full dose oxaliplatin
d. 50 % reduced dose of carboplatin

Case #2 Follow up and Discussion: Correct Answer: d

Cisplatin is a well-known nephrotoxin, and so the alternative regimen of carboplatin plus paclitaxel was employed. Carboplatin is not only less nephrotoxic but also slightly less efficacious than cisplatin in non-small cell lung cancer [12]. The reduction in dose by 50 % is recommended secondary to her estimated CrCl of 30–45 ml/min. The use of oxaliplatin is currently not recommended as first line therapy non-small cell lung cancer [13]. She tolerated chemotherapy with only mild toxicity and stable kidney function, but unfortunately her cancer recurred a year after her initial surgery, when she died from an intracerebral hemorrhage related to brain metastases.

Although it is impossible to state whether optimal adjuvant therapy with a cisplatin-based regimen would have resulted in cure, this case highlights the complexity of balancing pharmacokinetics, nephrotoxicity, and anticipated efficacy, when choosing chemotherapy in patients presenting with diminished kidney function. This can be especially challenging when chemotherapy is potentially curative, such as in this situation.

Case #3

A 29-year-old man presented with asymptomatic swelling of his right knee initially thought to be from excessive exercise. Subsequent workup revealed the presence of a high-grade synovial sarcoma, for which he was started on chemotherapy with ifosfamide with good response. However, after several months of treatment, his creatinine increased from 1.2 to 2.1 mg/dL and was thought to be related to ifosfamide. Ifosfamide was therefore discontinued but his renal function continued to worsen to the point where hemodialysis

was initiated. A few weeks later, his renal function gradually improved and hemodialysis was stopped. The oncologist wanted to coordinate care with you regarding re-initiation of ifosfamide now that his renal function has improved to a creatinine of 2.2 mg/dL (Cockcroft Gault 31 ml/min).

What is the next course of action in treating his sarcoma taking into mind his kidney function?

a. He should be given an aggressive IV fluid hydration regimen prior to chemotherapy.
b. Ifosfamide can be restarted at a regular dose, since he is now off hemodialysis.
c. Ifosfamide can be restarted with the dose adjusted according to his kidney function.
d. Low dose cisplatin can be combined with ifosfamide

Case #3 Follow up and Discussion: Correct Answer c

Ifosfamide is an alkylating agent which is used in treating germ cell tumors and sarcomas. It is structurally similar to cyclophosphamide. As such, one of the metabolites of ifosfamide, acrolein is particularly toxic to the bladder, causing hemorrhagic cystitis. Its other metabolite, chloracetaldehyde, is known to be directly toxic to the renal tubules, particularly the proximal tubules (causing proximal renal tubular acidosis/Fanconi syndrome and nephrogenic diabetes insipidus). Similarly, it has also been suggested [14] that ifosfamide leads to increased expression of cytochrome p450 enzymes in the kidneys and this may play a role in metabolizing ifosfamide into its toxic metabolites [14]. Although mesna, a synthetic sulfhydryl compound, has been traditionally administered concurrently with ifosfamide or cyclophosphamide to mitigate bladder toxicity (by preventing accumulation of the metabolite, acrolein), it is unclear as to whether or not it has any renoprotective role. Interestingly, it has been suggested in animal models [15] that N-acetylcysteine may have a protective role against ifosfamide nephrotoxicity. Intensive intravenous fluid hydration may not be the best option since dialysis was recently discontinued and the patient might have problems with fluid overload and fluid retention. In a study of children with unilateral nephrectomy [16], the incidence of ifosfamide nephrotoxicity was significantly increased and this is likely due to an already compromised renal excretory capability. See ifosfamide dose adjustment based on CrCl: Table 6.1:

Antineoplastic Agents in CKD
CrCl 46-60: Decrease dose by 20 %
CrCl 30-45: Decrease dose by 25 %
CrCl 10-29: Decrease dose by 30 %
Dialysis: No data

At present, there is limited pharmacokinetic data alluding to dialysis clearance of ifosfamide. Latcha et al. [17] recently published a case series of three ESKD patients (on maintenance hemodialysis) who were administered escalating doses of ifosfamide for metastatic sarcoma with a therapeutic responses and improvement in radiographic abnormalities. They also utilized a modified hydration protocol to mitigate against volume overload and bladder toxicity. The addition of cisplatin to ifosfamide can lead to additive nephrotoxicity and is therefore not recommended [18].

Drug Management in Patients with Cancer and Chronic Kidney Disease

A. Drug Absorption With oral drugs, the bioavailability of a drug is dependent upon drug absorption through the gastrointestinal (GI) tract. The most important factors associated with absorption of oral drugs include gastric transit time, emptying time, acid secretion, microbe content, enzyme content in the gut (e.g., CYP34A), and availability of gastric enzymes [19]. Drug absorption generally occurs by diffusion across a concentration gradient from areas of highest concentration (gastrointestinal mucosa) to areas of lower concentration (blood plasma). Absorption can occur against a concentration gradient through active transport. The milieu within the GI tract lumen may directly affect the absorption of many drugs into the body [20]. For instance, calcium-based phosphate binders such calcium carbonate and calcium acetate—commonly administered in patients with CKD—may alter oral bioavailability and downstream clinical pharmacokinetic parameters such as maximum concentration in the blood, area under the concentration–time curve (AUC), time to maximum concentration and half-life of many chemotherapeutic agents. For agents with cytotoxicity that depends on encountering cancer cells at specific points within the cell cycle, the area under the AUC is more important than peak drug concentration. By contrast, peak concentration is more important for other agents. Thus, any alteration of pharmacokinetics—starting with absorption—can potentially affect the cytotoxicity of these agents. Some oral chemotherapeutic agents are weak acids or weak bases, and therefore the pH of gastrointestinal contents can affect their absorption. Many patients with moderate to severe CKD may concomitantly take proton pump inhibitors (PPIs) or H_2 blocking agents. Thus increasing the pH of the gastrointestinal contents and contributing to decreased absorption of certain drugs thereby leading to decreased efficacy (such as erlotinib) [21]. Since the non-ionized (more lipid-soluble) form of a drug is more readily absorbed than the ionized form, acidic drugs are usually more readily absorbed in the upper regions of the gastrointestinal tract, where they are primarily in a non-ionized form [22]. For instance, estramustine (an antimicrotubule chemotherapy used to treat prostate cancer) can combine with many cations (e.g., Ca^{2+}, Mg^{2+}, Al^{3+}, and Fe^{2+}) in the GI tract to form poorly

absorbed complexes. Thus, certain foods (e.g., milk) or drugs (e.g., antacids, products containing Mg^{2+}, Al^{3+}, and Ca^{2+}salts, or Fe^{2+} preparations) can significantly decrease the absorption of chemotherapeutic agents [23]. Interestingly, reports linking PPIs to impaired kidney excretion of intravenously administered methotrexate through mechanisms that are not well understood, but that are unlikely related to PPIs alkalinizing effect in the stomach [24].

Some chemotherapeutic agents (e.g., azathioprine and 6-mercaptopurine) require first-pass metabolism to be activated following oral administration and absorption [25]. First-pass metabolism occurs when drugs pass from the gastrointestinal tract to the liver, where enzymes metabolize a fraction or the entire drug, thereby changing the drug's therapeutic activity in the body (either from activation of the drug, as mentioned above, or from inactivation in other cases). Ultimately, the dosing of an oral medication is strongly affected by the degree of first-pass metabolism it undergoes [25]. One can infer that any changes involving first-pass metabolism could significantly influence the degree and duration of exposure to the chemotherapeutic agent.

B. Drug Distribution Drug distribution is the second component of the pharmacokinetic triad. Drug distribution, elimination, and excretion can influence drug of choice and dosing and can be a factor in potential serious drug reactions and interactions. Volume of distribution (V_d) describes how chemotherapeutic agents are apportioned throughout the body depending on the three key variables: the inherent membrane permeability of the tissue and drug plasma protein binding, and storage capacity [26] of the tissue bed.

The permeability of basement membranes (e.g. the gastrointestinal blood capillary or the blood/brain barrier) determine if a specific drug will be able to pass through the basement membranes to reach the drugs target site. Lipophilic drugs represent 75 % of all drugs; these agents are more capable of passing through membranes by passive diffusion to the blood, while hydrophilic drugs require transport channels along the membrane and employ an adenosine triphosphate (ATP)-mediated active transport or facilitated diffusion.

Protein binding of the drug is another major variable in drug distribution. Proteins that commonly bind to chemical agents in the blood include albumin, globulins, and lipoproteins [27, 28]. In patients with CKD, in particular nephrotic syndrome (i.e., hypoalbuminemia), the percentage of drug that is bound by protein varies widely. However, the percentage of drug bound by protein does not necessarily impact the physiological effect of the agent. But, protein binding does affect the free fraction of drug. When drugs are largely protein bound, hypoalbuminemia may have a deleterious effect if a large amount of chemotherapeutic agent is circulating unbound in the systemic circulation. In addition, the presence of pleural effusions and ascites (due to third spacing of fluids) may significantly alter the terminal half-life of medications. Third-spaced fluid collections can also alter tissue penetrations of drugs with particularly small volumes of distribution but not for those with large volumes of distribution. The resulting prolongation of plasma half-life may be associated with unanticipated toxicity. Methotrexate is a classic example of a drug that can be sequestered in third-space fluid collections, resulting in persistence of drug in the body and severe toxicity if such fluid collections are not drained prior to administration [29].

Storage capacity is a term used to describe the maximum possible drug concentration at the site of action. A better therapeutic outcome will be achieved when the drug reaches the site of action more readily to exert its pharmacotherapeutic effect. Conversely, adverse drug reactions can occur if the drug accumulates in other tissues such as cardiac, liver, or kidney [30].

Drug interactions can also affect drug distribution especially when two or more drugs compete for the same protein-binding site. Affinity describes the tightness of a particular chemical to a receptor site, and drugs that bind tightly with a specific receptor site are said to have a high affinity. The drugs with high affinity will displace drugs that have a lesser affinity, resulting in the drug with higher affinity exerting more effect than the drug with the lower affinity at the same doses.

C. Drug Metabolism Most drugs undergo metabolism, which transforms the structure of the drug to a more hydrophilic agent before elimination from the body. The liver is the primary organ involved with drug metabolism, although other body systems such as the kidneys, lungs, and gastrointestinal tract may impact drug metabolism as well [19, 31]. In general, there are two phases of drug metabolism that occur in the liver: phase I and phase II. Phase I metabolism consists mainly of enzymes in the cytochrome P450 class (CPY). CPY-mediated metabolism, along with other phase 1 enzyme reactions, provide important pathways whereby the cell makes drugs into more polar and, thus, more easily eliminated compounds. Phase I involves oxidation or reduction through hydrolysis reaction by the CPYs. The CPYs are located in hepatocytes and many other cell types. Subfamily of CPYs known as CYP1, CYP2, and CYP3 metabolize 90 % of drugs [32]. Enzyme expression of CYPs are heavily influences by genetic polymorphisms. In fact, an individual's CYP genotype will determine the extent of drug metabolism of a particular agent with a strong predilection for CYP metabolism. In addition, other drugs or chemicals can either inhibit or enhance the rate of drug metabolism by altering CPY activity [33]. Therefore, inhibiting or enhancing CPY activity can lead to profound alteration in downstream drug concentration and activity [34]. Metabolic inhibition may delay the metabolism of chemotherapeutic agents typically leading to a buildup of the drug in the body and eventually leading to drug toxicity or serious adverse events. Conversely, CPY inhibition can prevent activation of pro-drugs, which are inactive forms of a drug that must be metabolized to their active form in order to have a therapeutic benefit [32]. An important example is codeine and more potent codeine derivatives, which are used for pain management in cancer patients and require CPY metabolism to become active analgesics in the body. CPY induction is also an important factor that over time leads to the need for dosage adjustment. For example, rifampin has good bioavailability, but over time induces CPY that is used for its own metabolism leading to increased clearance and decrease plasma levels. Hence, both CPY inhibitors and inducers can affect the metabolic action of multiple drugs, leading to either non-therapeutic results or harmful toxicity, respectively. Cyclophosphamide can be extensively metabolized by CPY to form 4-hydroxy-cyclophosphamide which is ultimately converted to phophoramide mustard, a toxin. Patients with certain fungal infection and taking fluconazole and itroconazole may have higher exposure to many toxic metabolites due to the drug's ability to down regulate CYPs which leads to the need for chemotherapy and other drug dosage adjustments [35].

Phase II metabolism occurs in medications that are unable to be excreted after completion of phase I metabolism. Phase II, therefore, acts on the resultant metabolites of phase I. These compounds are conjugated to proteins in the liver into larger molecules, which inhibits reabsorption from the tubules of the nephron [36]. After conjugation, most resulting complexes are inactive, but for those substances that result in active metabolites, accumulation can lead to toxicity.

Finally, drug elimination occurs in both the kidney and the liver. In the case of the former, following transformation to a hydrophilic agent, drug metabolites are excreted through urine. For the latter, drug metabolites from the liver are usually glucuronidated, incorporated into bile, and subsequently excreted in feces. Some enzymes found in the small intestine remove conjugated glucuronide, resulting in active drug, which is available for reabsorption and consequent delayed drug clearance [36, 37].

Therapeutic drug monitoring via plasma concentration measurements offers an opportunity to circumvent some of the extreme variability that results from such complicated pharmacokinetics, particularly in patients who are ill and in whom the usual pharmacokinetics for individual drugs may be deregulated. Unfortunately, reliable assays for testing most drugs do not exist. Furthermore, when assays exist, limited information is available regarding how plasma concentrations affect clinical endpoints such as efficacy and toxicity. For drugs that have a narrow therapeutic target range or are subject to significant pharmacokinetic variability, drug concentrations should be measured when possible to avoid toxicity and/or improve efficacy (Table 6.1).

D. Renal Clearance of Drugs Drug elimination is the process of metabolism and excretion and removal from the body. The majority of medications are eliminated via excretion by the kidneys. Some chemotherapeutic agents are excreted unchanged through the kidney, such as cisplatin and carboplatin, whereas others are metabolized to active or toxic metabolites and eliminated through kidney. Kidney excretion of metabolites occurs through three synergistic mechanisms: (1) glomerular filtration: passive diffusion from blood into the glomeruli of the kidney, (2) tubular secretion: active secretion from the proximal tubule or other nephron segments into the urine, and (3) tubular reabsorption: passive reabsorption of lipid soluble drugs in nephron segments.

When considering drug excretion, the regular monitoring of kidney function is an important and crucial first step for treating a patient with CKD who is receiving chemotherapy. Careful adjustment of drug dosing in patients with CKD and malignancy is often required. Although there are certain limitations, the calculated GFR through a 24-h creatinine clearance or estimated GFR by different methods are generally accepted ways to measure kidney function [38]. Either of these two indicators can be used for: (1) early detection of kidney impairment in cancer patients with risk factors, (2) evaluation of progression of CKD, (3) prognosis for preservation of current level of kidney function, (4) determining the need for dosage adjustment, and (5) determining the need for renal replacement therapy.

Table 6.1 Antineoplastic agents in chronic kidney disease [47–55]. The details on nephrotoxicities of some of these agents are listed in a different chapter

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Arsenic trioxide	No adjustment needed	No adjustment needed	Drug exposure may be higher, monitor for toxicity, and lower doses may be required	Not studied in hemodialysis patients	Case reports on acute tubular necrosis has been reported
Bleomycin	No adjustment needed	50–40 mL/min reduce dose by 30 % 40–30 mL/min reduce dose by 40 %	30–20 mL/min reduce dose by 45 % 20–10 mL/min reduce dose by 55 %	CRRT: reduce dose by 25 %	
Capecitabine (xeloda)	No dose reduction	25 % dose reduction	Contraindicated Note: has been used at 50–80 % dose reduction [2, 3]	Contraindicated Note: has been used at 50–80 % dose reduction [2]	No reports of nephrotoxicity
Carboplatin	No adjustment needed	Reduce dose by 50 %	Reduce dose by 50 %	HD: reduce dose by 50 % CAPD: Reduce dose by 75 % CRRT: dose at 200 mg/m^2	Nephrotoxicity often appears as hypomagnesemia (reversible tubular injury), and is most common in pts previously treated with cisplatin
Carfilzomib (kyprolis)	Reduced initial dose 15 mg/m^2 daily on Cycle 1, 20 mg/m^2 on Cycle 2, and 27 mg/m^2 on Cycles 3 and beyond	Reduced initial dose 15 mg/m^2 daily on Cycle 1, 20 mg/m^2 on Cycle 2, and 27 mg/m^2 on Cycles 3 and beyond	Reduced initial dose 15 mg/m^2 daily on Cycle 1, 20 mg/m^2 on Cycle 2, and 27 mg/m^2 on Cycles 3 and beyond	Reduced initial dose 15 mg/m^2 daily on Cycle 1, 20 mg/m^2 on Cycle 2, and 27 mg/m^2 on Cycles 3 and beyond; dosed after dialysis	Rises in serum creatinine appear prerenal, with rises in BUN as well.Cases of acute renal failure have also been reported in the setting of myeloma progression or renal impairment at baseline(prerenal, tumor lysis, and thrombotic microangiopathy have been reported)

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Carmustine (BiCNU)	Insufficient data	Insufficient data	Avoid	Avoid	Progressive azotemia, increased serum creatinine, and renal failure reported during and after discontinuation of prolonged therapy of over 1 year and at least six cycles. Decreased kidney size, membranous nephropathy, tubular atrophy, and glomerular sclerosis have been reported after cumulative doses over 1.5 g [11–12]. Indirect nephrotoxicity may occur secondary to infusion-related hypotension
Cetuximab	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Nephrotoxicity often appears as hypomagnesemia (tubular injury)
Chlorambucil (Leukeran)[15]	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment	No reports of nephrotoxicity
Cisplatin	Reduce dose by 25 %	Reduce dose by 50 %	Reduce dose by 50 % or consider use of alternate agent	HD: reduce dose by 50 %, and administer after HD CAPD: Reduce dose by 50 % CRRT: reduce dose by 25 %	Per manufacturer recommendation cisplatin should not be administered to any pt with preexisting renal impairment Nephrotoxicity often appears as renal failure, renal tubular acidosis, and hypomagnesemia (tubulointerstitial injury). Prevention with aggressive hydration, forced dieresis, and cytoprotective agents (amifostine)
Cladribine	No adjustment needed	Reduce dose by 25 %	Reduce dose by 25 %	CAPD: reduce dose by 50 %	Very limited data on dose adjustments in renal insufficiency. Use with caution

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Clofarabine (clolar)	50 % dose reduction	50 % dose reduction	Insufficient data	Insufficient data	Nephrotoxicity can present as proteinuria or rapid-onset acute renal failure with proteinuria
Crizotinib	No adjustment needed	No adjustment needed	Administer 250 mg Qday	Not studied in dialysis patients	Tubular toxicity has been reported
Cyclophosphamide	No adjustment needed	No adjustment needed	No adjustment needed	CrCl < 10 mL/min but not on dialysis reduce dose by 25 % HD: Reduce dose by 50 % and administer after HD CAPD: Reduce dose by 25 % CRRT: No adjustment needed	Nephrotoxicity often appears as hyponatremia (SIADH and increased N/V) and hemorrhagic cystits. Prevent hyponatremia with adequate hydration and mesna. Prevent hemorrhagic cystitis with adequate hydration, and morning dosing (reduces time of medication in the bladder at night)
Cytarabine (high dose 1-3 g/m^2)	Reduce dose by 40 %	Reduce dose by 50 %	Consider alternative agent or dose 100–200 mg/m^2/day CIV	No data	Renal adjustments are only required in high doses (1–3 g/m^2)possibly for > 500 mg/m^2
Dacarbazine (DTIC)	Insufficient data	Insufficient data	Insufficient data	Insufficient data Case report of successful use of 100 mg IV x 5 days every 4 weeks	Mild to moderate azotemia without permanent damage

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Daunorubicin	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Mainly excreted through the bile, however per FDA recommendations at 50 % dose reduction is recommended in pts with a SCr > 3
Epirubicin	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Mainly excreted through the bile, however per FDA recommendations at 50 % dose reduction is recommended in pts with a SCr > 5
Eribulin	Reduce to 1.1 mg/m^2/dose	Reduce to 1.1 mg/m^2/dose	No data	No data	
Erlotinib (Tarceva)	Insufficient data	Insufficient data Note: hold if CrCl < 30 due to treatment	Insufficient data Note: hold if CrCl < 30 due to treatment	Insufficient Data Note: hold if CrCl < 30 due to treatment	Renal impairment or failure may follow hepatic impairment (hepatorenal syndrome) or severe dehydration
Etoposide	Reduce dose by 15 %	Reduce dose by 20 %	Reduce dose by 25 %	HD: reduce dose by 50 % (not removed by HD) PD: reduce dose by 50 % (not removed by PD) CRRT: reduce dose by 25 %	
Fludarabine	Reduce dose to 20 mg/m^2	Reduce dose to 20 mg/m^2	Avoid use	HD: administer after hemodialysis CAPD: Reduce dose by 50 % CRRT: Reduce dose by 25 %	About 50 % of every dose is excreted by the urine

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Gefitinib (Iressa)	No dose adjustment	No dose adjustment	No dose adjustment Note: use caution	No dose adjustment Note: use caution	No reports of nephrotoxicity Note: < 4 % renal elimination
Gemcitabine	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Nephrotoxicity often appears as hemolytic uremic syndrome (microangiopathic lesions)
Hydroxyurea (Droxia)	50 % dose reduction 7.5 mg/kg daily	50 % dose reduction 7.5 mg/kg daily	50 % dose reduction 7.5 mg/kg daily	50 % dose reduction 7.5 mg/kg daily; dosed after dialysis	Temporarily impaired tubular function with elevated serum uric acid, BUN, and creatinine
Ibrutinib (imbruvica)	No dose adjustment MCL: 560 mg po daily	No dose adjustment MCL: 560 mg po daily	Insufficient data	Insufficient data	Renal failure preceded by increases in creatinine of 1.5–3 times the upper limit of normal. Note: < 1 % excreted renally
Ifosfamide	Reduce dose by 20 %	Reduce dose by 25 %	Reduce dose by 30 %	No data	Nephrotoxicity often appears as fanconi syndrome, renal tubular acidosis, nephrogenic diabetes insipidus, and hemorrhagic cystitis. Prevent nephrotoxic effects by maintaining adequate hydration, using mesna, and monitoring electrolytes

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Imatinib	No adjustment needed	CrCl 59–40 mL/min max recommended dose of 600 mg	CrCl 39–20 mL/min reduce starting dose by 50 %, increase as tolerated. Max recommended dose 400 mg	CrCl < 20 mL/min use caution, 100 mg has been tolerated in some pts	18 % of the drug is excreted through the urine
Interferons	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Nephrotoxicity often appears as proteinuria, (minimal change, and acute tubular necrosis)
Interleukin-2	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Nephrotoxicity often appears as prerenal azotemia from renal hypoperfusion (capillary leak syndrome). Prevent renal complications by controlling volume and hemodynamic status. Avoid other nephrotoxins
Irinotecan	No adjustment needed	No adjustment needed	No adjustment needed	HD: reduce dose from 125 mg/m^2–50 mg/m^2	Use with caution in renal insufficiency. Although only small amounts of irinotecan are present in the urine several case reports have shown toxicity in pts with ESKD. Use with caution

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Lenalidomide	MCL: dose 10 mg daily MDS: dose 5 mg daily MM: dose 10 mg daily	MCL: dose 10 mg daily MDS: dose 5 mg daily MM: dose 10 mg daily	MCL: dose 15 mg Q48H MDS: dose 2.5 mg daily MM: dose 15 mg Q48H	HD: MCL: dose 5 mg (after HD) MDS: dose 2.5 mg (After HD) MM: dose 5 mg (after HD)	Patients with multiple myeloma frequently have renal insufficiency. T1/2 and AUC increase as creatinine clearance decreases
Lomustine	Reduce dose by 25 %	Reduce dose by 30 %	Avoid use	Avoid use	Nephrotoxicity often appears as a slowly progressive, chronic interstitial nephritis, which is generally irreversible, and can be induced by prolonged therapy time. First signs of renal involvement are elevations in SCr, followed by proximal tubular damage (usually proteinuria, and renal tubular acidosis). Nephrotoxicity may be delayed from several months to as long as several years after discontinuation
Melphalan	Reduce dose by 15 %	Reduce dose by 25 %	Reduce dose by 30 %	Limited data	Nephrotoxicity often appears as SIADH. Have pts maintain adequate hydration during therapy
Methotrexate	Reduce dose by 35 %	Reduce dose by 50 %	Avoid use	CRRT: reduce dose by 50 %	Nephrotoxicity often appears as non-oliguric renal failure (intratubular deposition of methotrexate). Avoid nephrotoxicity with aggressive hydration with NS, urine alkalinization, and forced diuresis (3 L/day)

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Mitomycin	Limited data	Limited data	CrCl < 10 mL/min reduce dose by 25 %	CAPD: reduce dose by 25 %	Nephrotoxicity often appears as hemolytic uremic syndrome (4–6 % of pts) via microangiopathic lesions. It is most likely to appear after at least 6 months of therapy, and is related to cumulative dose
Oxaliplatin	No adjustment needed	No adjustment needed	Reduce dose from 85 mg/m^2–65 mg/m^2	Limited data	Nephrotoxicity rarely appears as acute tubular necrosis, however, the significance is much less than the previous generation platins (cisplatin and carboplatin)
Paclitaxel (taxol)	No dose adjustment[14] 135 or 175 mg/m^2	No dose adjustment[14] 135 or 175 mg/m^2	No dose adjustment[14] 135 or 175 mg/m^2	No dose adjustment[14] 135 or 175 mg/m^2	Mild to severe elevations in serum creatinine may occur, particularly in patients with Kaposi's Sarcoma Note: < 12 % renal excretion[29]
Panitumumab	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Nephrotoxicity often appears as hypomagnesemia (tubular injury). Monitor electrolytes and supplement Mg
Pemetrexed	No adjustment needed	Limited data avoid use	Limited data avoid use	Limited data avoid use	Nephrotoxicity rarely occurs, but appears as acute tubular necrosis, renal tubular acidosis, and diabetes insipidus
Pentostatin	Reduce dose by 30 %	Reduce dose by 40 %	Consider an alternative agent	Limited data	

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Rituximab	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Pts with high circulating tumor cells (> 25,000/mm^3) or with a high tumor burden are at an increased risk of developing tumor lysis syndrome. Prophylaxis should be considered in high risk pts
Sorafenib	Reduce dose to 400 mg BID	Reduce dose to 200 mg BID	Limited data	HD: reduce dose to 200 mg daily	Nephrotoxicity often appears as proteinuria, and nephrotic syndrome (renal thrombotic microangiopathy)
Streptozocin	No adjustment needed	Reduce dose by 25 %	CrCl < 10 mL/min reduce dose by 50 %	Limited data	Nephrotoxicity often appears as a slowly progressive, chronic interstitial nephritis, which is generally irreversible, and can be induced by prolonged therapy time. First signs of renal involvement are elevations in SCr, followed by proximal tubular damage, usually proteinuria (65–75 %). Nephrotoxicity may be delayed as long as several years after discontinuation
Sunitinib	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Nephrotoxicity often appears as proteinuria, and nephrotic syndrome (renal thrombotic microangiopathy)
Temozolomide (temodar)	Insufficient data Note: pharmacokinetics equivalent for CrCl 36–130 ml/min	Insufficient data	Insufficient data	Insufficient data	No reports of nephrotoxicity

Table 6.1 (continued)

Drug	CrCl 60–46 mL/min	CrCl 45–30 mL/min	CrCl 29–10 mL/min	Dialysis	Nephrotoxicity presentation/comments
Topotecan	Reduce dose by 20 %	Reduce dose by 25 %	Reduce dose by 30 %	Limited data	
Vandetanib	Reduce initial dose to 200 mg daily	Reduce initial dose to 200 mg daily	Reduce initial dose to 200 mg daily	Limited data	Nephrotoxicity rarely occurs, but appears as increased SCr, and proteinuria
Vemurafenib (zelboraf)	No dose adjustment 960 mg po every 12 h Note: clearance similar to patients with normal renal function	No dose adjustment 960 mg po every 12 h Note: clearance similar to patients with normal renal function	Insufficient data	Insufficient data	Case series of nephrotoxcities have been reported (acute tubular necrosis) mainly
Vinca alkaloids	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed	Nephrotoxicity often appears as hypernatremia secondary to SIADH. Maintain adequate hydration during treatment

The gold standard for measuring GFR is to determine it directly by intravenously injecting the polysaccharide inulin [39]. Inulin is neither excreted nor reabsorbed by the kidney thus making it the best indicator of GFR. However, it is time consuming, cumbersome to perform, and expensive to obtain. When precise GFR measurements are required in clinical practice, they are usually indirectly performed via measurements of creatinine clearance (CrCl) in a 24-h urine specimen [CrCl = Urine Cr conc (mg/dL) × Urine vol (mL)/Serum Cr conc (mg/dL) × time (min)]. Creatinine, a product of skeletal muscle, is both freely filtered by the glomerulus and secreted by the renal tubules. Limitations of 24-h urine assessments include the fact that it overestimates GFR by 16 % [40], and 24-h urine collections, are both time consuming and subject to significant error.

Given the practical challenges of 24-h urine collections, eGFR determinations using serum creatinine and more recently other metabolites such as cystatin C are more commonly employed. The Cockroft–Gault (CG) equation is one method used to determine CrCl by measuring serum creatinine, age, gender, and weight [41]. Limitations to this process include: (1) overestimation of CrCl and (2) weight variability from edema or obesity may over estimate CrCl requiring use of ideal body weight or adjusted body weight instead of actual body weight. Creatinine levels are also affected by such factors as tubular secretion, muscle mass, and diet. This can pose a problem for elderly patients who, typically, have decreased muscle mass [42].

CG Equation CrCl (mL/min) = [(140 − age) × Weight in kg/(SCr × 72) × (0.85 if female)] Ideal body weight (IBW) is used unless actual body weight (ABW) < IBW. If ABW is > 30 % of IBW, adjusted body weight is used where: adjusted body weight = [(ABW−IBW) x 0.4[4]] + IBW. IBW male = 50 + 2.3 × (height in inches − 60); IBW female = 45.5 + 2.3 × (height in inches − 60)

A second method, the modified diet in renal disease (MDRD) equation estimates kidney function (eGFR) using patient demographics (age, gender, and ethnicity), serum creatinine, urea nitrogen, and albumin concentrations. The MDRD method is an effective screening tool for kidney dysfunction. Many drug dosing recommendations have been determined in studies based on CrCl and not eGFR, making the CG method the preferred method for adjusting medications based on kidney function [43].

For obese men and women the equation should be modified [44]:

$$(\text{obese men}) = \frac{(137\text{-age}) \times \left[(0.285 \times \text{wgt}) + (12.1 \times \text{hgt}^2)\right]}{51 \times \text{Scr}}$$

$$(\text{obese men}) = \frac{(146\text{-age}) \times \left[(0.287 \times \text{wgt}) + (9.74 \times \text{hgt}^2)\right]}{60 \times \text{Scr}}$$

wgt = patient's weight in kg

hgt = patient's height in cm

Modification of Diet in Renal Disease Re-Expressed Equation (MDRD) eGFR MDRD = 175 x SCr−1.154 x Age−0.203 × (0.742 if female) x (1.21 if AA), AA refers to African American

Finally the chronic kidney disease epidemiology collaboration (CKD-EPI) equation is another effective screening tool for estimating kidney function; however, CKD-EPI is largely limited also by eGFR's relatively unproven utility in determining drug dosing [45].

Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) eGFR CKD-EPI = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)−1.209 × 0.993 Age × 1.018 [if male] × 1.159 [if African American], where κ is 0.7 for females and 0.9 for males, α is− 0.329 for females and − 0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1

The most common drug dosing recommendations are based on pharmacokinetic studies that use creatinine clearance estimates by the CG equation for a measure of kidney function. Nowadays, the MDRD equation is most commonly used in the clinical setting to assess kidney function as well as to stratify and classify CKD. However, healthcare professionals should proceed cautiously when using these equations especially in extremes of weight and age. Use of a conservative kidney function estimate, such as the CG equation, may be desired especially when prescribing drugs with a narrow therapeutic index in order to prevent toxicity and maximize efficacy [46]. The recommendations below are according to CrCl as estimated by the CG equation and this is a good starting point for dose adjustment in the presence of CKD.

E. Medication Dose Adjustment for Impaired Kidney Function Healthcare providers caring for patients with cancer and CKD should adjust antineoplastic agents that are impacted by renal insufficiency according to the CrCl. Table 6.1 provides a starting point for drug adjustment for most commonly used antineoplastic agent. However, the adjustments listed in the table should not replace the patient specific factors and the clinical judgment of healthcare providers. During acute changes in kidney function (indicated by changes in urine output and serum creatinine), CG equations and other measures of estimated GFR are unreliable as serum creatinine is a delayed indicator of acute kidney injury. Furthermore, CrCl calculations might significantly overestimate patient's kidney function and healthcare providers should use their clinical judgment regarding these changes. Therefore, patients with cancer pose a significant challenge for employing effective medication management when AKI is present, thus altering drug elimination. Dosage adjustment is essential to avoid drug toxicities and maximize the likelihood of a positive therapeutic outcome.

F. Medication Administration in Patients with ESKD on Renal Replacement Therapy There many factors that influence drug removal during dialysis: (1) type and frequency of dialysis, (2) molecular weight (MW) of drug, (3) protein binding, (4) hydrophilicity of drug (solubility and chemistry), and (5) finally dialysate composition and blood flow. Typically, peritoneal dialysis (PD) results in minimal drug removal (approximately 10 % of drugs are cleared using PD). However, hemodialysis (HD) can result in significant drug removal (approximately 30–50 %). Patients on PD who have cervical cancer are uniquely suited to have chemotherapeutic agents administrated through their PD access. Drugs that are highly protein bound are more readily removed with PD than with HD due to significant protein loss observed in the

peritoneal exchanges. Furthermore, drugs having a > 70 % protein bound component or with a large volume of distribution (> 2 L/kg) have lower plasma concentration and, therefore, an insignificant amount of drug will be removed during HD. In general, drugs with small MW can be removed effectively through diffusion during HD treatments. However, drug removal during HD is most commonly achieved passively through a concentration gradient that forms between the high drug concentration in the plasma and the low drug concentration of the dialysate. Therefore, drug removal during HD is dependent on the surface area, pore size, and composition of the dialysis membrane composition dialysate and blood flow rates. In contrast, large MW drugs are removed less efficiently as clearance depends on convective forces. As drugs with larger MW are removed during HD it will take longer to equilibrate the drug from intra or extracellular compartments and may result in significant post-dialysis rebound. Unfortunately, there is very limited information about how some chemotherapeutic agents are cleared by HD or PD. Therefore, a majority of the recommendations are based on the molecular size, volume distribution, and protein binding of the drug.

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Chapter 7
Electrolyte Disorders in Cancer Patients

Sheron Latcha

List of Abbreviations

ADH	Antidiuretic hormone
ATN	Acute tubular necrosis
AVN	Avascular necrosis
BP	Bisphosphonates
CaSR	Calcium sensing receptor
CrCl	Creatinine clearance
CRRT	Continuous renal replacement therapy
eEGFR	Epithelial growth factor receptor
FSGS	Focal segmental glomerular sclerosis
HM	Hypercalcemia of malignancy
HPT	Primary hyperparathyroidism
IHD	Intermittent hemodialysis
IL	Interleukin
MM	Multiple myeloma
MCD	Minimal change disease
M-CSF	Macrophage colony stimulating factor
OB	Osteoblast
OC	Osteoclast
OPG	Osteoprotegerin
PTH-rP	Parathyroid hormone-related protein
RANK	Receptor activator of nuclear factor kappa B
RANK-L	Receptor activator of nuclear factor kappa B ligand
SIADH	Syndrome of inappropriate antidiuretic hormone
SCLC	Small cell lung cancer
TBW	Total body water

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TLS	Tumor lysis syndrome
TNF-α	Tumor necrosis factor-α
VEGF	Vascular endothelial growth factor

The spectrum of fluid and electrolyte disorders in oncology patients has some important and distinct features when compared to those of the general population. Electrolyte disorders in cancer patients can be related to chemotherapy agents, a paraneoplastic component of the cancer or patient related factors. Hyponatremia is observed with greater frequency in oncology patients, and it's pathogenesis in this population can be exclusive to the malignancy itself or to the chemotherapy given to treat the disease. Similarly, hypomagnesemia can be attributable to chemotherapeutic agents like cisplatin, ifosfamide, and cetuximab, and thus is seen only in cancer patients. Hypercalcemia of malignancy is another important oncologic diagnosis that is discussed in this chapter. Additionally, there are a number of spurious electrolyte disorders associated with liquid malignancies, which the hematologists, oncologists, and nephrologists need to be familiar with. This chapter describes the frequency of the most commonly observed electrolyte disorders in the cancer patients and delves into the unique cancer or chemotherapy-related etiology of these clinical problems.

Case #1
A 38-year-old female with metastatic breast cancer (bone, liver) presents to her usual outpatient visit and is reported to be hypotensive, tachycardic, and confused. She is afebrile and there are no focal neurologic deficits. Laboratory tests reported a creatinine concentration of 2.6 mg/dl and serum calcium of 14.6 meq/L. She was admitted with a similar presentation 3 weeks prior. At that time, the 25-OH and 1,25-OH vitamin D levels were normal, parathyroid hormone (PTH) was low and PTH-related protein (PTH-rp) was above normal. She was admitted and given intravenous (IV) 0.9 % calcitonin, and zoledronic acid. Similar treatment was given during her prior hospitalization. She was discharged 3 days later with normal serum calcium and creatinine values and her confusion was entirely resolved. At her follow-up clinic visit 7 days after discharge, the patient's laboratory tests reported a serum creatinine value of 1.7 mg/dl and a calcium value of 12.5 mEq/L. What is the best way to manage this patient?

a. IV hydration with normal saline (NS)
b. Diuretics
c. Bisphosphonates
d. Calcitonin
e. Denosumab

Hypercalcemia of malignancy (HM), which was reported in up to 30 % of cancer patients, is the most common life-threatening electrolyte disorder in this population

[1]. Following this diagnosis, the prognosis from this malignancy-related complication is poor. Prior to bisphosphonate therapy, the average life expectancy following this diagnosis was about 30 days [2]. This number has increased to about 60 days since the advent of bisphosphonates [3]. Skeletal metastases with resultant HM can occur in association with any advanced cancer, but has been most frequently reported with neoplasias of the lungs, breasts, kidneys, and with multiple myeloma (MM). In postmortem studies, up to 75 % of these patients have bone metastases at death. Bone is the most common site for metastases in prostate cancer, affecting up to 90 % of patients with advanced disease. On the contrary, skeletal metastases are uncommon with tumors of the head and neck, lymphomas and malignancies of the pancreas, liver, and colon [4, 5].

Numerous factors account for this propensity for skeletal metastases by various tumors. Bone marrow stoma-tumor interactions are crucial in the pathogenesis of bone metastases, and the normal high blood flow to areas of red marrow fosters the critical interchange of various adhesive and angiogenic factors. Adhesive and angiogenic factors like vascular endothelial growth factors (VEGF) allow tumors to bind to bone marrow stromal cells and to bone matrix and establish a blood supply. Tumoral cytokines like PTH-rP, various interleukins (IL), and macrophage colony stimulating factor (M-CSF) then promote local bone resorption [6]. The bone itself is a stockpile of inactive growth factors that are released and activated during bone resorption. These released growth factors in turn propagate additional tumor cell expansion [7–9].

A brief discussion of normal bone homeostasis helps to understand the pathogenesis of HM. The principal participants in normal bone remodeling include three cell types (bone marrow stromal cells, osteoblasts [OB], and osteoclasts [OC]), and three proteins (receptor activator of nuclear factor kappa B [RANK], receptor activator of nuclear factor kappa B ligand [RANK-L], and osteoprotegerin [OPG]). See Fig. 7.1. OCs are derived from myeloid precursors and promote bone resorption. RANK, a protein complex that controls the transcription of DNA, is found in almost all cell types, including OCs. RANK is activated by RANK-L, a member of the TNF superfamily and a key osteoclastogenic cytokine which is produced mainly by bone marrow stromal cells and OBs. When RANK-L binds its receptor RANK on OC progenitor cells, this promotes osteoclastogenesis, OC proliferation, OC activation, and consequently, bone resorption. RANK-L activity is inhibited by OPG, a soluble decoy receptor for RANK-L. Bone homeostasis thus relies on the balance between bone resorbing (RANK-L binding to RANK) and bone protecting (RANK-L binding to OPG) interactions. Activated T cells and numerous pro-inflammatory cytokines (interleukins 1β and 6 [IL-1β, IL-6]I, tumor necrosis factor-α [TNF-α]), all found in the neoplastic milieu, have been shown to promote RANK-L driven bone resorption, thereby perturbing the RANK/RANK-L/OPG balance [10].

Bone metastases have been characterized predominantly as osteoblastic or osteoclastic. In actuality, the majority of metastatic bone lesions involves both OC and OB activity, but with a dysregulation in the normal balance between OB and OC activity. For example, although most patients with breast cancer have predominantly OC-mediated bone destruction, there is secondary OB bone formation in response

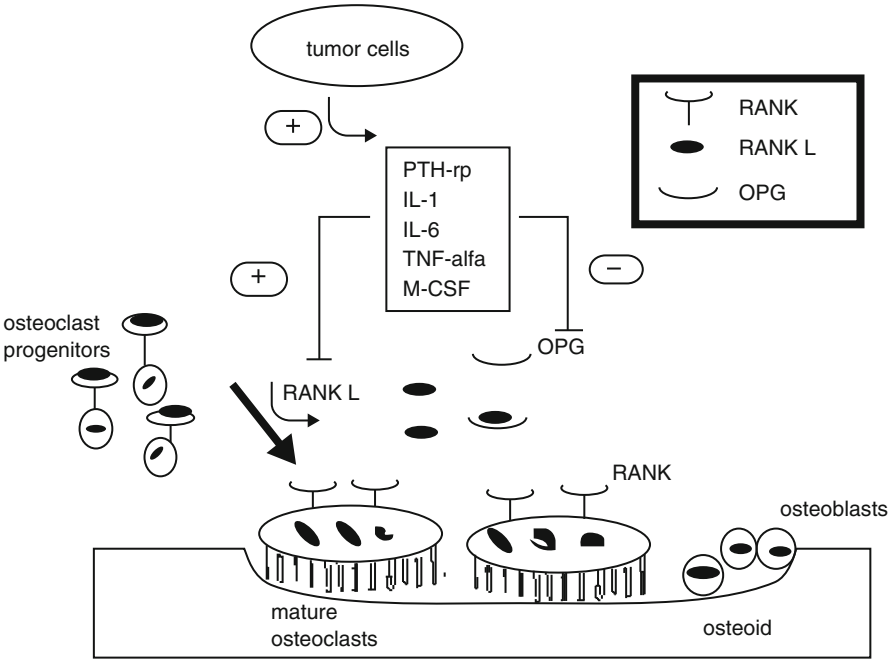

Fig. 7.1 The principal participants in normal bone remodelling include three cell types (bone marrow stromal cells, osteoblasts [OB], and osteoclasts [OC]) and three proteins (receptor activator of nuclear factor kappa B [RANK], receptor activator of nuclear factor kappa B ligand [RANK-L], and osteoprotegerin [OPG]). OCs are derived from myeloid precursors and promote bone resorption. RANK, a protein complex that controls the transcription of DNA, is activated by RANK-L, a member of the TNF superfamily and a key osteoclastogenic cytokine which is produced mainly by bone marrow stromal cells and OBs. When RANK-L binds its receptor RANK on OC progenitor cells, this promotes osteoclastogenesis, OC proliferation, OC activation, and consequently, bone resorption. RANK-L activity is inhibited by OPG, a soluble decoy receptor for RANK-L. Activated T cells and numerous pro-inflammatory cytokines (interleukins 1β and 6 [IL-1β, IL-6]I, tumor necrosis factor-α [TNF-α]), and macrophage colony stimulating factor (M-CSF), all found in the neoplastic milieu, have been shown to promote RANK-L driven bone resorption, thereby perturbing the RANK/RANK-L/OPG balance

to osteolysis [11]. Similarly, while metastatic prostate cancer is associated with predominant osteoblastic lesions, there is increased bone resorption at the sites of these osteoblastic lesions[12]. Uniquely, multiple myeloma (MM) can cause purely lytic bone lesions. Indeed, bone scans of patients with MM and severe osteolytic lesions are normal in up to half of all patients [13]. RANK-L and macrophage inhibitory protein 1α, potent inducers of OC formation, appear to be the key mediators in bone destruction in these MM patients [14–16].

While a number of humeral factors present in the neoplastic milieu have been identified to promote bone resorption, PTH-rp accounts for an overwhelming majority of cases. PTH-rp production has been reported to be the pathogenetic mechanism in up to 88 % of cases of HM. PTH-rp was found in 92 % of breast cancer patients

with bone metastases [17]. Local osteolysis and vitamin D production together accounted for the remaining 12 % of cases [18]. When vitamin D production is reported as the cause of HCM, it has been most often associated with lymphomas and MM.

PTH-rp is a protein member of the parathyroid hormone family and has biological roles in development of mammary glands, lactation, endochondral bone formation, and islet function. There is homology between PTH and PTH-rp at the amino terminal end, but the divergence in the remainder of the molecule accounts for their immunologic distinctiveness. There is no cross reactivity between the assays for PTH and PTH-rp. Like PTH, PTH-rp can stimulate OC activity; increase renal calcium absorption in the loop of Henle and distal convoluted tubule, and stimulate vitamin $1,25(OH)_2$ production. Interestingly, there is a higher incidence of cancer in patients with primary hyperparathyroidism (HPT), and of primary HPT in patients with cancer. Therefore, it is recommended that both the PTH and PTH-rp be checked in cancer patients since primary HPT portends a better prognosis and requires specific therapy [19, 20].

Hypercalcemia can affect the neuropsychiatric, cardiac, gastrointestinal, and renal systems. From a renal standpoint, the relevant clinical manifestations include nausea, lethargy, acute kidney injury, polyuria, and thirst. Polyuria develops because the high serum calcium levels activate calcium sensing receptors (CaSR), which in turn, results in decreased transport of NaCl in the loop of Henle, and consequently, a decrease in the countercurrent mechanism and a decline in renal concentrating ability. Moreover, activation of the CaSR blunts the response to antidiuretic hormone (ADH) in the collecting duct [21]. The resulting polyuria induces volume contraction and stimulates thirst. These patients often cannot hydrate themselves adequately due to hypercalcemia induced nausea, vomiting, and lethargy. Hypercalcemia induced vasoconstriction of the renal blood vessels, coupled with volume contraction, can both contribute to acute kidney injury in these patients.

The primary goals in the management of hypercalcemia are to (1) increase urinary excretion of calcium and (2) inhibit OC bone resorption. To this end, in the absence of edema, aggressive volume resuscitation with isotonic NS to promote a urine output of 100–150 cc/h is recommended. These patients are often significantly dehydrated and may require several liters of isotonic saline to restore their intravascular volume deficit. Once the patient is adequately volume replete, furosemide can be used to promote a calciuresis. It is recommended that furosemide should not be given prior to volume resuscitation, since the diuretic can further compromise the patient's hemodynamic status. Calcitonin can begin to lower serum calcium within 4–6 h of administration, with a maximum effect of 1–2 mg/dL (0.3–0.5 mmol/L) [22, 23]. It does so by inhibiting bone resorption and OC maturation, and by increasing urinary calcium excretion. Unfortunately, tachyphylaxis due to downregulation of it receptors occurs after repeated dosing, thus the medication loses efficacy after 48 h [24]. In patients who are volume overloaded or anuric, dialysis with a low calcium dialysate (2.5 mEq/L) may be necessary to manage HM.

Since receiving the FDA approval for treatment of osteolytic bone metastases in the 1990s, bisphosphonates (BP) have become a cornerstone for management of HM. Pamidronate and zoledronate currently have FDA approval for the management

of HM. Ibandronate is available but does not have this FDA indication. BPs inhibit OC function via both intracellular and extracellular mechanisms. The BP molecule is structurally similar to native pyrophosphate molecules that normally adhere to hydroxyapatite crystal-binding sites on the bone surface, especially in areas undergoing active resorption. The BP molecules reduce osteoclast activity by preventing the OCs ability to adhere to the bone surface; to form the ruffled border; and to produce the proteins necessary for continued bone resorption [25–27]. At the intracellular level, BPs inhibits farnesyl diphosphate synthase in the mevalonate pathway, resulting in decreased OC progenitor development and recruitment by promoting OC apoptosis [28]. Since the onset of action of BP is 2–4 days, it is recommended that they be administered at the time that HM is recognized. Their nadir effect is evident at days 4–7 [1].

The farnesyl diphosphate synthase pathway is also present in human renal proximal tubular cell lines, and this may in part explain the acute tubular necrosis (ATN) and Fanconi's syndrome that has been reported following exposure to BPs. Other well known renal complications of this class of drugs include collapsing focal segmental glomerular sclerosis (FSGS) and minimal change disease (MCD). Collapsing FSGS has been predominantly described with the use of pamidronate, and with few exceptions, most of these patients progressed to end stage renal disease requiring dialysis [29]. Avascular necrosis (AVN) of the jaw, and at other areas of high occlusal force, due to over suppression of OC bone turnover, has also been reported following BP exposure. Collapsing FSGS and AVN has been more frequently reported in cases when the BP was administered in excess of the recommended dose. Consequently, current recommendations are that BPs should not be dosed more frequently than every 3 weeks. Even though pamidronate has been associated with nephrotic syndrome and collapsing FSGS, it appears to be relatively safe when appropriately dosed in patients with chronic kidney disease [30]. Zolendronate is more often associated with renal tubular toxicity [29].

For pamidronate, the current dosing guidelines for patients with a creatinine clearance (CrCl) < 30 cc/min is the usual 90 mg dose to be given over 4–6 h. Zoledronate is contraindicated in patients with a CrCl < 30 cc/min. For those patients with a CrCl between 30–60 cc/min, dose of zoledronate should be reduced, with no dose adjustment for pamidronate. To date, intravenous ibandronate has not been reported to cause renal toxicity [31]. However, as stated previously, the drug does not yet have an FDA approval for treating HM.

Following BP therapy, 60–90 % of patients achieve normocalcemia for a 1–3 week period following drug administration. Given the potentially devastating clinical consequences associated with exceeding the recommended dosing guidelines for BPs, managing those patients who have HM that is resistant to BP therapy can be challenging. For those patients who present with hypercalcemia within that 3 week period following the last dose of BP. HM that is resistant to BP may be due to inadequate bone resorption [32–34]. Also, PTH-rp augments renal calcium absorption, and this may explain recurrent hypercalcemia shortly after BP therapy [35].

Researchers have investigated therapeutic strategies for the management of HM that is resistant to BP therapy. The most promising agent is denosumab, a fully humanized monoclonal antibody against RANK-L. Urinary and serum N telopeptide levels start to decrease within 1 day of exposure to denosumab and this effect lasts for up to 64 days. The onset and duration of these indices following pamidronate dosing are 3 and 28 days, respectively [36]. Currently, the recommended dose of denosumab is 120 mg SQ every 4 weeks. Importantly, this drug does not yet have an FDA approval for the treatment of HM. It does have an FDA approval for prevention of skeletal related events in bone metastasis from solid tumors. The agent has no known nephrotoxic effects but has been reported in association with AVN of the jaw [37] and can cause severe hypocalcemia [38]. Presently, there is an ongoing clinical trial on the treatment of HM in subjects with elevated serum calcium despite recent treatment with IV BPs (ClinicalTrials.gov Identifier**:**NCT00896454). Another agent which has been used to treat HCM and those with parathyroid cancer is cinacalcet. This agent binds to calcium sensitive receptors (CaSR) on tumor cells and downregulates PTH synthesis and therefore decreases serum calcium [39]. This drug is not FDA approved for treating HM.

Case #1 Follow Up and Discussion:
The patient was started on IV hydration with NS. Once well hydrated over 24 h, the patient was given furosemide to promote calcium loss in the urine. This will acutely correct the hypercalcemia. This patient has HM that is resistant to BP therapy. Since a BP was given less than 2 weeks ago, it is not advisable to retreat with BP at this time. The patient does have bone metastasis, and therefore, can be given denosumab 120 mg SQ every 4 weeks for the indication to decrease skeletal related events. Note that denosumab does not yet have an FDA approval for managing BP resistant HM.

Hyponatremia

Case #2
A 25-year-old male with a nonseminomatous germ cell tumor who completed his first cycle of cisplatin and ifosfamide 5 days ago was brought to the ER for nausea, vomiting, and confusion. Significant vital signs reported upon presentation are a blood pressure of 90/54 mm/Hg and a heart rate of 140 beats/min. He responded appropriately to his name but could not answer questions appropriately. Initial laboratory tests show a sodium concentration of 109 mEq/L,

creatinine 3 mg/dl (was 1.0 mg/dl at baseline), serum osmolarity 235 mOsm, urine osmolarity 650 mOsm, urine sodium 174 mEq/L, normal TSH, and a slightly elevated serum cortisol value. At the time of examination, he had received 2 L of 0.9 % NS. His blood pressure was 95/50, heart rate 120, and sodium concentration was stable at 109 meq/L.

What is the cause of hyponatremia in this patient and what is the appropriate treatment?

a. Syndrome of inappropriate antidiuretic hormone (SIADH)
b. Hypovolemic hyponatremia from gastrointestinal losses
c. Renal salt wasting syndrome related to cisplatin
d. Adrenal crisis

Hyponatremia has been observed in up to 46 % of hospitalized cancer patients, and when present, is associated with a poor prognosis compared with euvolemic patients, regardless of tumor type [40–46]. The reported incidence varies greatly, and is affected by the cancer type and the cutoff point for serum used to define hyponatremia. Hyponatremia has been reported most frequently with small cell lung cancer (SCLC) [47]. The syndrome of inappropriate antidiuretic hormone release (SIADH) is the most common cause of hyponatremia in cancer patients, with higher rates among those with SCLC than with other malignancies [48, 49]. Ectopic antidiuretic hormone (ADH) can be produced by tumors, chemotherapeutic agents, pain and nausea, and by other medications commonly prescribed in this population. Even though SIADH is a common cause of hyponatremia in cancer patients, these patients are also at increased risk for hypovolemic hyponatremia from volume contraction due to vomiting, diarrhea, and salt-wasting nephropathy.

There are two important points to keep in mind when approaching disorders of serum sodium: (1) Disorders of serum sodium are essentially disorders of serum osmolarity, and (2) disorders of serum sodium are disorders of relative concentrations of salt and water since serum sodium is expressed in mEq/L. So, even in the patient who has hypovolemic hyponatremia, there is an excess of total body water (TBW) relative to total body sodium.

To elaborate on the first point, disorders of serum sodium can be approached as disorders of serum osmolarity since serum osmolality = 2 Na + Glucose/8 + BUN/2.8. Therefore, in a euglycemic patient, serum sodium essentially equals serum osmolality. Serum osmolality is normally tightly maintained between 280–290 mOsm/L and within 1–2 % in a particular individual. Osmoreceptors located in the anterior hypothalamus detect serum osmolality, and, under physiologic conditions, an increase in serum osmolarity causes release of ADH from the posterior pituitary. In the kidneys, ADH binds to V2 receptors on the basolateral membrane of collecting ducts cells to promote insertion of aquaporin-2 channels to the apical membrane. Increased free water permeability of the apical membrane promotes free water absorption, and consequently, reduces serum osmolality closer to the normal range. ADH also stimulates thirst at higher values of serum osmolality. In the hyperosmolar patient, the

end effect of ADH release is increased free water retention. The other physiologic stimulus for ADH release is a decline in plasma volume of $> 7–9\,\%$ [50, 51]. These systems are bimodal and importantly, in the absence of an elevated serum osmolality or a significant decrement in plasma volume, ADH should not be released. Therefore, to make the diagnosis of SIADH, the patient should be euvolemic and have a normal serum osmolality.

An algorithm for evaluating these patients is proposed in Fig. 7.2.The first step in evaluating the patient with hyponatremia is to measure the serum osmolality. Hyperosmolar hyponatremia in cancer patients can occur in the setting of procedures like hysteroscopy or transurethral resection of the prostate. During these procedures, large volumes of nonconductive flushing solutions containing glycine are used to create a surgical field within the body cavity. The large volumes of these solutions create elevated pressures within the body cavity. This allows osmotically active particles like glycine to translocate into the venous circulation. Osmotically active particles in the extracellular space cause movement of water from the intracellular to the extracellular space to equalize the osmotic gradient across the cell membrane. As a result, the serum sodium decreases due to dilution. Hyponatremia can occur via the same mechanism when intravenous immune globulin is given in a maltose or sucrose solution, or when patients are hyperglycemic or given mannitol.

A normal serum osmolality in a hyponatremic patient signifies that the patient has pseudohyponatremia. As the moniker suggests, these patients have a normal serum osmolality and normal serum sodium, but, due to the presence of excessive amounts of lipids or paraproteins in circulation, there is a reduction in the fraction of serum that is water and an artificially low serum sodium concentration is measured. With the newer ion specific electrode method, this miscalculation should not be an issue. It is important to identify this category of patients since they require no further therapy for hyponatremia.

After excluding the patient with hyperosmolar hyponatremia and pseudohyponatremia, the remaining patients fall into the category of hypoosmolar hyponatremia. Since this group lacks an osmolar stimulus for ADH release, the only physiologic stimulus for ADH release would be a significant decrement in plasma volume. Therefore, determining the volume status in these patients, as well as measuring the urine osmolality and urine sodium, will help to identify the etiology of the dysnatremia, as well as provide information on the appropriate treatment for this group.

Assessing the volume status in cancer patients can be challenging. Edematous patients may actually have intravascular volume depletion if the edema is the result of a pelvic mass compressing the lymphatic system; if it is due to a deep venous thrombosis or to IVC compression; or if the patient has a capillary leak syndrome from the malignancy itself. Patients with liver metastasis as a cause of hepatorenal syndrome can also have significant ascites and edema on examination, but have significant intravascular volume depletion due to vasodilation within the splanchnic circulation. Resting tachycardia can be a misleading sign of volume contraction since these patients experience pain, anxiety, and discomfort. Therefore, when feasible, checking orthostatic blood pressures can provide valuable information on the volume status of these patients.

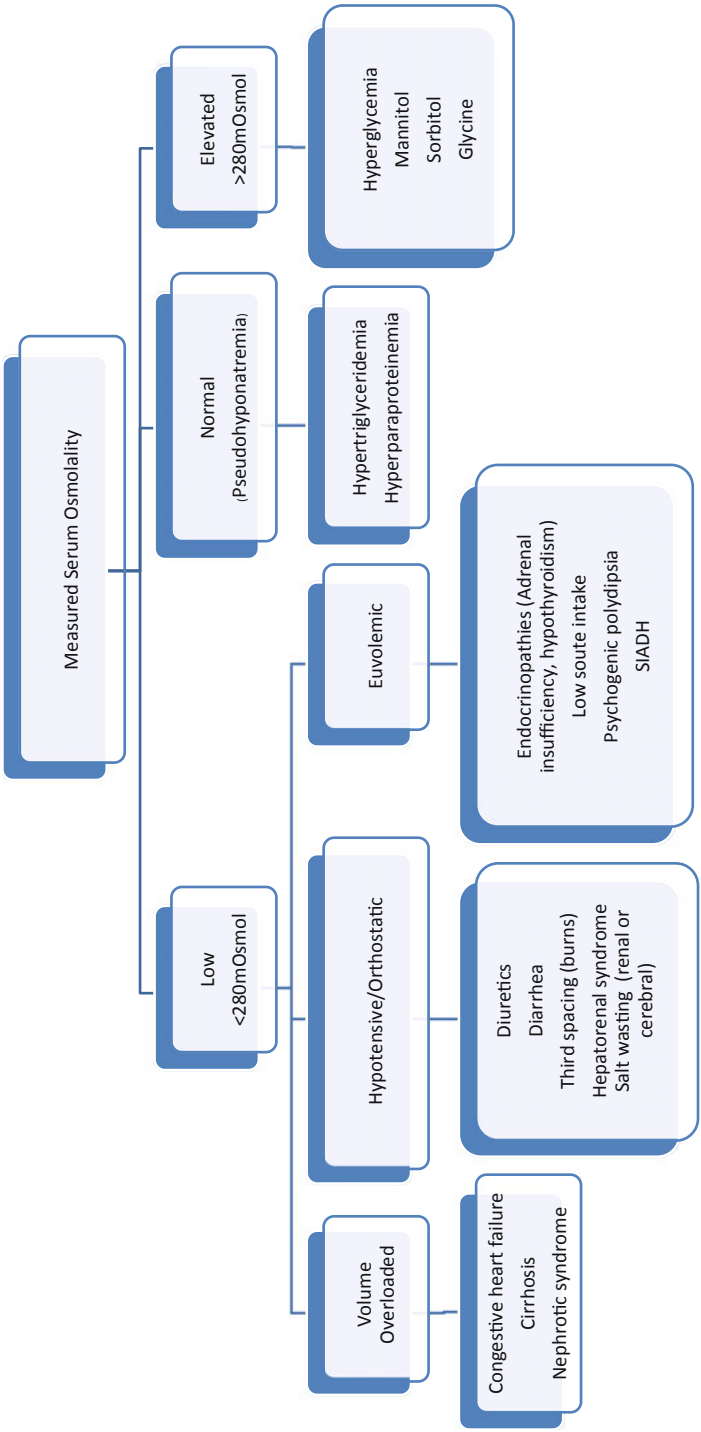

Fig. 7.2 Algorithm for the evaluation of hyponatremia

Since all hyponatremia cases are essentially disorders of relative concentrations of salt and water, with relatively more TBW than salt, knowing the volume status of the patient can help to clarify the pathogenesis of the electrolyte disorder. In the hypervolemic patient, total body salt and TBW are both increased. In the hypovolemic patient, both are decreased but there is relatively more TBW than sodium. In the euvolemic patient, TBW and sodium are fairly normal but these patients do have slightly more TBW than salt, but no appreciable edema.

As stated previously, the diagnosis of SIADH can only be made in a patient who has a normal serum osmolality and normal plasma volume. In patients with SCLC, the tumor itself is the source of inappropriate ADH release. Additional etiologies of inappropriate ADH release in cancer patients include pain, nausea, and chemotherapy. Chemotherapeutic agents can alter central ADH secretion and its effects in the renal tubules. Vincristine and vinblastine are directly toxic to the hypothalamic pituitary axis and disturb the normal osmotic regulation of ADH secretion [52, 53]. Cisplatin and cyclophosphamide both induce ADH release, and the latter also potentiates ADH effect in the kidney. Commonly prescribed medications like tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase inhibitors, and opioids stimulate ADH secretion. Nonsteroidal anti-inflammatory medications potentiate ADH effect in the renal tubules [53]. Conditions associated with cancer can also cause SIADH and include CNS or pulmonary diseases, such as subarachnoid hemorrhage, pneumonia, mechanical ventilation, and metastasis of the lungs and brain [51].

In the patient with hypovolemic hyponatremia, a review of the patient's history and medication list will often reveal the source of their volume deficit. Volume losses from diarrhea, diuretics, or hyperglycemia are easily identified. A cause of hypovolemic hyponatremia that warrants special attention in cancer patients is salt-wasting nephropathy. Cisplatin and ifosfamide directly injure renal tubule cells, thereby impairing renal sodium reabsorption [54, 55]. Cerebral salt wasting due to metastatic CNS disease, surgery, and trauma has also been described. Hyponatremia due to either nephrogenic or cerebral salt wasting may be difficult to distinguish from SIADH, since the urine osmolality and urine sodium can be elevated relative to the serum values. Importantly, patients with either type of salt wasting become volume contracted if their urinary losses of salt and water exceed the amount that they are able to ingest orally. Clinically, patients with salt wasting are hypotensive and/or orthostatic on examination, whereas the patients with SIADH appear euvolemic.

The clinical signs and symptoms of hyponatremia are in large part manifestations of increased intracerebral pressure due to brain edema. When the serum sodium and serum osmolality are lower than that within the brain cells, water shifts into the brain cells. Since the skull is a fixed cavity, it cannot expand to accommodate this increase in brain volume. Some clinical signs of increased intracranial pressure include nausea, confusion, vomiting, decline in mental status, ataxia, and seizures. If the brain volume markedly exceeds the skull volume, frank herniation of the brainstem occurs. There are adaptive mechanisms in place to mitigate brain edema in the setting of hyponatremia. When the serum sodium drops too rapidly relative to the ability of the brain to adapt to the change in osmolality, clinical signs and

symptoms develop. This explains why one patient presents seizures and another can appear asymptomatic at equivalent serum sodium values.

The brain's adaptive mechanisms are essentially aimed at decreasing its water content back to normal by extruding solute. In rat models, Na^{2+} and Cl^{-} are extruded via the Na^{2+} and Cl^{-} channels present in the cell membrane within 30 min of induction of hyponatremia. These electrolyte losses are maximal at around 3 h. After longer periods of persistent hyponatremia, organic osmolytes like glutamate, creatine, and taurine exit the brain cell [56]. These compensatory adaptations explain why rapid correction of chronic hyponatremia leads to rapid egress of water from the brain cells. In mild cases, dehydration of the brain tissue occurs, and in severe cases, osmotic demyelination can occur. The current recommendation is that the serum sodium should not be corrected more than 12 mEq/L within the first 24 h, and generally, at a rate of not more than 0.5 mEq/L/h [51].

The severely symptomatic hyponatremic patient who are euvolemic or hypervolemic and are present with seizures, impaired mental status, or coma should be managed in consultation with a nephrologist and/or a critical care specialist. These patients require frequent neurological evaluations and monitoring of their serum sodium values while they receive 3 % NS. Importantly, the severely symptomatic patient with hyperosmolar hyponatremia should not receive 3 % NS. Administration of hypertonic solutions in this setting is contraindicated as they worsen the hyperosmolar condition in such patients. These patients may require urgent dialysis. Patients with significant hypovolemia should be treated with boluses of NS until a euvolemic state is achieved. Thereafter, the rate of correction of the serum sodium should not exceed 10–12 mEq/L in a 24 h period.

For patients with hypoosmolar hyponatremia who are minimally symptomatic, the appropriate treatment depends largely on their volume status and on the disease state that is responsible for their volume status. Hypervolemic hyponatremia due to iatrogenic volume overload is best managed by minimizing all intravenous solutions, with or without the addition of diuretics. Patients with congestive heart failure are best managed by minimizing all salt containing intravenous solutions (NS, Normosol, Lactated Ringers, and half NS) and with the use of diuretics. Furosemide is the diuretic of choice in the treatment of hyponatremia, since thiazide type diuretics can actually cause hyponatremia. The aquaretic agents, conivaptan and tolvaptan, have been shown to increase serum sodium by 6–8 mEq/L within a 48 h period without the hypokalemia and accompanying metabolic alkalosis that can result from treatment with diuretics [57].

The management of the asymptomatic patients with euvolemic hypoosmolar hyponatremia is a bit more multidimensional. If nausea, vomiting, and pain are stimulating ADH, then appropriate use of antiemetics and pain medications can diminish these nonphysiologic stimuli for ADH release. Any of the culprit medications that have been implicated as a cause of hyponatremia (see Fig. 7.3) should be discontinued if it is safe to do so. Additional interventions are all aimed at decreasing the relative concentrations of salt and TBW in the patient. Patients can be asked to restrict their fluid intake to 1–1.5 L of free water per day. Patient compliance with fluid restriction can be difficult since they are frequently told to "stay well hydrated"

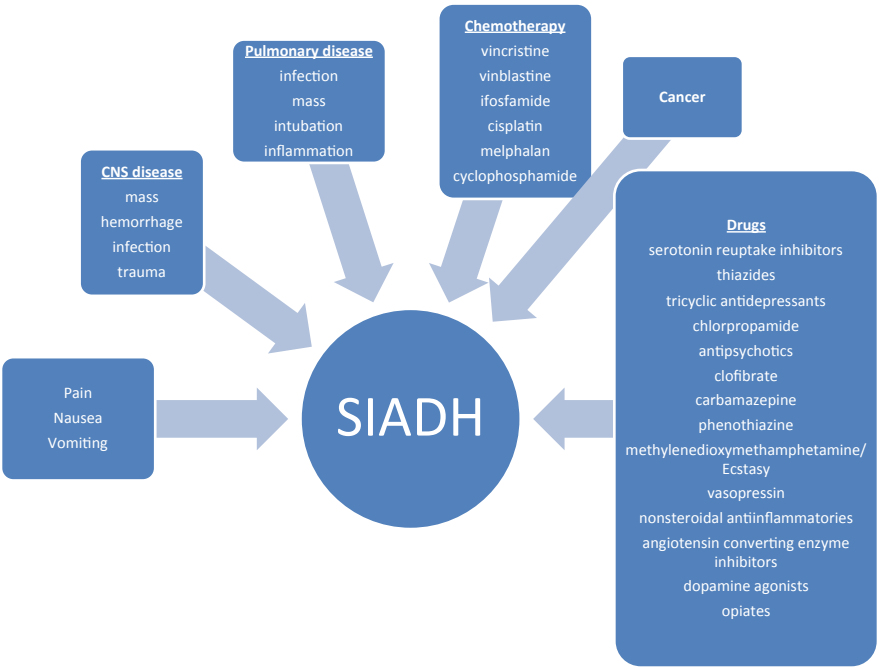

Fig. 7.3 Causes of the syndrome of inappropriate antidiuretic hormone (SIADH)

while on chemotherapy and because their pain medications and antidepressants can make them dipsogenic. Therefore, adjunctive pharmacologic therapy is frequently needed. In patients whose blood pressures can tolerate it, furosemide can be used to increase free water losses via the urine. Usual doses in patients with normal renal function are 10–20 mg per day. In euvolemic patients, NaCl tablets can be administered as well. V2 receptor antagonists are the new class of agents which can be used in the management of hypervolemic and euvolemic hyponatremia. V2 receptor antagonists block ADH-mediated insertion of aquaporin channels at the apical membrane of the collecting duct cells. Consequently, free water is lost in the urine. The currently available intravenous and oral formulations in the USA are conivaptan and tolvaptan, respectively. Although tolvaptan is administered orally, the package insert states that the medication needs to be started in the inpatient setting in order to check serial serum sodium values so that overly rapid correction of hyponatremia can be properly identified and managed. In a small study of cancer patients, tolvaptan was shown to be safe and to have superior efficacy in controlling hyponatremia when compared with standard therapy using fluid restriction, diuretics, and salt tablets. No patients overcorrected [58]. Any combination of fluid restriction, NaCl tablets, furosemide, and/or a V2 receptor antagonist can be used to achieve a normal serum sodium value in this group of patients.

Case #2 Follow Up and Discussion

Cisplatin and ifosfamide can both cause salt-wasting nephropathy. Correct answer is (c).

A diagnosis of SIADH is not tenable in the presence of hypotension and volume depletion. Patients with SIADH have elevated urine osmolarity in the absence of low urine sodium, and they are, by definition, normotensive (since hypotension would be a cause of appropriate ADH release). Moreover, when patients with SIADH are treated with 0.9 % NS, the serum sodium value typically decreases as they excrete the infused sodium in the NS (to be in sodium balance as their total body sodium is normal), but retain the water in the NS because of the inappropriate ADH, and as a result, the persistently open water channels. This patient would be best managed with an admission to the ICU. He can be given 0.9 %NS until he is no longer hypotensive, in order to avoid hemodynamic collapse. At that point, the serum sodium should be rechecked. Thereafter, the serum sodium can be corrected using 0.9 %, 2 %, or 3 % NS to correct the serum Na, but not more than 10–12 mEq/L over a 24 h period. Patients like this may require oral sodium chloride tablets, midodrine, and fludrocortisone to maintain normal serum sodium and blood pressure until the salt wasting resolves.

Case #3

A 58-year-old female with metastatic breast cancer (brain, bone, liver) on paclitaxel is admitted for dizziness, palpitations and is found to be orthostatic on examination. She reports recent onset of urinary frequency and nocturia (up to 4 times per night). She drinks about 64 ounces of fluids per day as instructed by her oncologist and has no diarrhea or fevers. Her UA shows no evidence of infection; the serum glucose is normal and the urine specific gravity and osmolarity are 1.002 and 141 mOsml/kg, respectively.

Which of the following best clarifies the diagnosis?

a. MRI of the abdomen/pelvis
b. Water deprivation test
c. MRI of the brain
d. Administer DDAVP

Hypernatremia

Hypernatremia can be conceptualized in a manner similar to hyponatremia in that establishing the relative concentrations of salt and water in the patient and the volume status of the patient yields the correct diagnosis. Patients receiving exogenous sodium (hypertonic saline, IV NS, oral NaCl tablets, IV sodium bicarbonate) tend to be volume overloaded and/or hypertensive because they have an excess of salt relative to free water. Patients who have lost free water in excess of salt are volume depleted and/or hypotensive. Examples of such cases include free water losses from the kidney (diuretics), skin (high fevers, excessive sweating), respiratory tract (ventilated patients), and from the GI tract (diarrhea, vasoactive intestinal peptide producing tumors, or VIPomas). In all of these cases, if the patient cannot match or exceed the free water losses, the serum sodium concentration rises.

Because of ADH's tight control of serum osmolarity within a very narrow range, when serum sodium increases (for example from 140–150 mEq/L) thirst is stimulated and individuals "drink themselves" back to a normal serum sodium. Therefore, hypernatremia develops when there is a defect in the synthesis or release of AVP from the pituitary (central diabetes insipidus, CDI) or unresponsiveness of the renal tubule to AVP (nephrogenic DI). The most common etiologies of CDI are neurosurgery, trauma, primary or metastatic tumors, and infiltrative diseases [59]. Leukemic infiltration of the pituitary stalk in patients with acute leukemias has also been reported to cause CDI [60, 61]. Most patients with CDI or NDI have a normal thirst mechanism and are also present with polydipsia. In the general adult population, the most common causes of NDI are chronic lithium use, hypokalemia and hypercalcemia [59]. In cancer patients, obstructive uropathy from masses at the bladder neck or ureter can also cause ADH unresponsiveness. Amyloid deposition along the basement membrane of medullary collecting ducts has been associated with unresponsiveness to AVP [62]. Chemotherapeutic agents and medications commonly used for the management of infectious complications following chemotherapy and bone marrow transplantation that have been associated with NDI include cidofovir, indinavir, tenofovir, foscarnet, amphotericin, ifosfamide, cyclophosphamide, methotrexate, and ofloxacin [63–67]. A water deprivation test can help to distinguish CDI from NDI and a detailed explanation of this test can be found elsewhere [59].

Hypervolemic or euvolemic hypernatremia can be managed with discontinuing exogenous salt containing IVFs and by correcting the free water deficit orally with free water or intravenously with 5 % dextrose water. There are numerous online calculators to measure the water deficit, or the following equation can be used:

Free water deficit $= 0.5^{*} \times$ *body weight (kg) [140/plasma sodium* $-1]$

**0.6 for lean males, 0.5 for females*

To avoid brain edema, which can occur if the deficit is corrected too rapidly, only half of the calculated water deficit should be administered within the first 24 h. The serum sodium should not be corrected more than 12 mEq/L over the initial 24 h. When correcting hypovolemic hypernatremia, the best approach is to re-expand the

intravascular volume with 0.9 % or 0.45 % NS until the patient is no longer orthostatic. For patients with ongoing GI, renal, and insensible fluid losses, a portion of these losses should be added to the calculated deficit. Concomitant hypercalcemia and hypokalemia needs to be corrected as both conditions are associated with unresponsiveness of the renal tubules to AVP.

Case # 3 Follow Up and Discussion
The patient is orthostatic on examination so a water deprivation test is not appropriate to evaluate for diabetes insipidus. Administration of DDAVP in a patient with hypernatremia, a dilute urine and hypotension can help to distinguish if the patient has CDI or a NDI. Choice (d) is the most appropriate answer.

Case #4
A 40-year-old male with colon cancer on chemotherapy with irinotecan and cetuximab presents for routine follow up. His only complaints are fatigue and occasional but bothersome "twitchiness" of his eyes and some muscle spasms. Routine serum chemistries are drawn and the only abnormality is a magnesium level of 0.9 mEq/L. His medications include hydrochlorothiazide and omeprazole.

Which chemotherapy agent is the most likely culprit for the hypomagnesemia?

a. Irinotecan
b. Cetuximab
c. Neither, it is the proton pump inhibitor
d. Neither, it is the diuretic leading to hypomagnesemia

Hypomagnesemia

Among the general hospital population, hypomagnesemia has been observed in up to 15 % of patients [68, 69]. The incidence of hypomagnesemia appears to be higher among hospitalized cancer patients, especially critically ill cancer patients, with reported frequencies of 17 and 46 %, respectively [70–73]. Hypomagnesemia, when present, may be associated with poorer clinical outcomes. One study that looked at hypomagnesemic and normomagnesemic groups with comparable APACHE II scores found that the mortality rates of the hypomagnesemic medical ICU and non-ICU groups were approximately twice the rate of the normomagnesemic groups [74].

Of note, hypomagnesemia may actually be underreported since the serum magnesium level is not reported as part of the routine chemistry panel.

The incidence and severity of hypomagnesemia is particularly high among patients who receive treatment with cisplatin and monoclonal antibodies directed against the epithelial growth factor receptor (eEGFR) domain (cetuximab, panitumumab). In a recent meta-analysis of the incidence of hypomagnesemia with cetuximab therapy, the incidence of all grade hypomagnesemia was 37 %. Panitumumab-induced hypomagnesemia was reported in 90 % of patients treated at one center [75]. Not infrequently, treatment with these agents has to be interrupted or stopped as a consequence of severe magnesium depletion. While patients receiving anti-EGFR therapy seem to respond to magnesium supplementation and maintain normal magnesium levels after the drug is stopped, a proportion of patients with ifosfamide- and cisplatin-related hypomagnesemia can have persistently low levels for years after cessation of drug treatment [76]. The incidence and severity of hypomagnesemia due to cisplatin and anti-EGFR therapy appear to be related to duration of exposure to these agents[77]. Other cancer drugs that can cause hypomagnesemia include cyclosporine, tacrolimus, pegylated liposomal doxorubicin, and interleukin-2. Other medications frequently given to cancer patients that can cause or potentiate hypomagnesemia include diuretics, aminoglycosides, amphotericin B, pentamidine, gentamicin, and proton pump inhibitors [69]. Proton pump inhibitors have been associated with hypomagnesemia (gastrointestinal loss of Mg) after prolonged use, usually more than a year [78–80].

Less than 2 % of the total body magnesium is present in the extracellular space, and only two third of this amount is unbound to albumin (free) and is active. The remainder of total body magnesium resides in bones and soft tissues, with the bones being the principal source of magnesium. The kidneys and the GI tract are the major organs of magnesium absorption and elimination from the body. Although magnesium depletion from GI losses can occur from upper or lower tract losses, lower tract secretions contain much larger magnesium content than upper tract secretions. (15 mEq/L in the lower tract versus 1 mEq/L in the upper tract) [81]. Thus, hypomagnesemia is more common with diarrhea, malabsorption, and short bowel resection compared with vomiting or nasogastric suction.

Magnesium elimination from the body occurs predominantly in the kidneys. In the setting of magnesium depletion, the kidneys fastidiously conserve magnesium, with the main site of magnesium reabsorption being the thick ascending limb of the loop of Henle. Magnesium handling in the kidney is slightly different than for other electrolytes in that the threshold for urinary excretion of magnesium is very close to the normal serum concentration of this electrolyte. Consequently, if a hypomagnesemic patient is receiving an IV bolus of magnesium and the serum magnesium rises abruptly, the kidneys quickly eliminate magnesium. For this reason, it is recommended that magnesium infusions should be given slowly to improve magnesium absorption and minimize renal elimination.

Hypokalemia and hypocalcemia can coexist with hypomagnesemia, so there is overlap between some of the clinical signs and symptoms of hypomagnesemia and deficiencies of these other electrolytes. Neuromuscular symptoms of magnesium deficiency include generalized weakness, tetany, seizures, delirium, and coma. Cardiac

manifestations include EKG changes (widening of the QRS complex, flattening of the T wave) and ventricular and atrial arrhythmias.

The severity of the clinical manifestations of hypomagnesemia and the extent of the deficiency determines the appropriate dose and route for magnesium repletion. In the setting of ventricular arrhythmias or EKG abnormalities, IV magnesium sulfate 1–2 g can be given as a bolus followed by a slow infusion once hemodynamic stability is achieved. For severe asymptomatic hypomagnesemia (serum magnesium less than or equal to 1 mg/dl or 0.4 mmol/L, 4–8 g of magnesium sulfate can be infused slowly over 12–14 h. For less significant deficiencies (serum magnesium levels > 1.2 mg/dl or 0.5 mmol/L) oral magnesium can be used, preferably using a sustained release preparation.

Case #4 Follow Up and Discussion
Cetuximab is a monoclonal antibody directed against the epithelial growth factor receptor, and has been reported to cause hypomagnesemia in up to 37 % of patients. Concomitant use of proton pump inhibitors and diuretics may exacerbate the level of hypomagnesemia. When possible, these medications should be discontinued if the cetuximab needs to be continued. Given the presence of neuromuscular irritability, this patient will require intravenous therapy with magnesium sulfate. Magnesium is best absorbed when it is delivered by slow infusion. This patient can be given 6–8 g of magnesium sulfate over 6–8 h. In addition, oral magnesium therapy should be started. He should continue to receive additional doses of IV magnesium if he continues to have neuromuscular irritability. Often times, for patient on cetuximab, oral repletion does not adequately maintain normal serum magnesium levels, even after IV repletion. These patients may require IV magnesium repletion to be given on a regular basis (once or twice weekly) for the duration that they are on cetuximab, in order to maintain normal serum magnesium levels. The hypomagnesemia usually resolves several weeks after the treatment with cetuximab is completed. The correct answer is (b).

Hypophosphatemia

Case #5
A 43-year-old female with breast cancer and diffuse bone involvement is admitted for failure to thrive, vomiting, and a small bowel obstruction (SBO). She has lost 15 kg over the past 1 month. On admission, laboratory tests show a serum albumin concentration of 2 g/dl, calcium 5.3 mEq/L, and phosphorus

1 mg/dl. She last received denosumab 1 day earlier. The SBO is found to be the result of mass effect of the tumor in the abdomen and the decision is made to initiate parenteral nutrition. Following electrolyte repletion, the calcium is 7.8 mEq/L, albumin 1.8 g/dl, and phosphorus is 1.4 mg/dl. Two days after starting parenteral nutrition, the patient complains for painful cramps in her legs, dark urine, and is found to have acute renal failure.

What is the diagnosis?

a. Rhabdomyolysis due to refeeding syndrome
b. Acute renal failure from denosumab
c. Bone pain and obstructive uropathy from progression of disease.

Severe hypophosphatemia (< 1.0 mg/dL)is relatively uncommon in the general hospital population, affecting only 0.4 % of hospitalized patients[82]. However, among hypophosphatemic patients, 6 % had a neoplastic process [83]. When present, severe hypophosphatemia is associated with significant risk of mortality but it commonly goes unrecognized and inappropriately treated [82].

Symptoms of hypophosphatemia generally occur at levels < 1.0 mg/dL and include myocardial dysfunction, respiratory failure, muscle weakness, rhabdomyolysis, and hemolysis. Seizures, coma, severe neuropathy, and paresthesias have also been reported [84]. These symptoms are likely due to the ATP deficiency since phosphorus, a predominantly intracellular mineral, exists in the body in organic phosphate compounds such as creatinine phosphate, adenosine phosphate (ATP), and 2,3-diphosphoglycerate (2,3-DPG). Decrease in ATP, the chief reservoir of biochemical energy, and 2,3-DPG, a moiety involved in oxygen release from hemoglobin in RBSs to tissues, accounts for the majority of symptoms of hypophosphatemia.

Decreased intestinal reabsorption of phosphorus, redistribution from the EC to the IC compartments, and increased renal excretion of phosphorus are all mechanisms of hypophosphatemia. Decreased dietary intake is a rare cause of hypophosphatemia unless there is a concurrent intake of phosphate binders [85]. Common causes for the redistribution of phosphorus from the EC to the IC space include respiratory alkalosis and refeeding syndrome (RFS). Respiratory alkalosis enhances phosphorus uptake by the muscle cells due to the decrease in intracellular CO_2 with subsequent stimulation of glycolytic pathway and increased production of sugar phosphates, which in turn lead to phosphate movement to the IC compartment. Conditions associated with respiratory alkalosis include sepsis, heat stroke, and liver disease [85]. Administration of enteral or intravenous nutrition to malnourished cancer patients can cause RFS, which is a massive shift of electrolytes, predominantly phosphorus, to the IC space due to increased IC requirement for phosphorus during tissue anabolism. RSF typically becomes evident 48–72 h after initiation of enteral or parenteral nutrition in an at-risk patient and has been described to cause life-threatening hypophosphatemia [86]. Hypophosphatemia due to increased anabolism and intracellular influx has also

been observed in patients with hematopoietic reconstitution after allogeneic stem cell transplantation and in leukemia patients with rapid tumor cell replication [85].

Renal phosphate wasting and resulting hypophosphatemia has been described in association with a number of chemotherapeutic agents. Although the mechanism of tubular injury is not completely understood, ifosfamide causes toxicity to the proximal tubular cells, leading to Fanconi syndrome. Mesna, which is administered for prevention of hemorrhagic cystitis, may contribute to this proximal damage [87]. The presentation is more common in children than in adults and is usually reversible, but permanent renal damage and hypophosphatemia may persist in 25–44 % of patients. Risk factors include cumulative dose of ifosfamide ($> 50\,mg/m^2$), preexisting renal disease, prior nephrectomy, younger age at treatment (< 5 year olds most at risk), diagnosis of Wilms tumor, and prior treatment with cisplatin. Cisplatin, carmustine, azacitidine, pamidronate, lenalidomide, and imatinib have all been reported to cause Fanconi syndrome as well [87–90]. Monoclonal gammopathies are also a cause of Fanconi syndrome and hypophosphatemia. Light chains, which are resistant to lysosomal degradation, deposit in the proximal tubules and impair their ability to reclaim electrolytes normally [91].

Imatinib, sunitinib, and sorafenib, all multi-target tyrosine inhibitors, purportedly induce hypophosphatemia via a different mechanism. By inhibiting platelet-derived growth factor receptors expressed on osteoclasts, these agents cause a subsequent decrease in bone resorption and decreased calcium and phosphate egress from the bone. Consequently, PTH levels increase and phosphaturia follows [92]. In clinical trials of IV bisphosphonates, the incidence of severe hypophosphatemia approached 50 % and was most common in patients treated for HM [93]. Denosumab, a monoclonal antibody that binds RANK ligand, has also been associated with hypophosphatemia, albeit much less frequently [94, 95].

Tumor-induced, or oncogenic osteomalacia is a rare disorder of renal phosphate wasting found in association with abnormal vitamin D metabolism, osteomalacia, and high levels of fibroblast growth factor 23 (FGF23). The hypophosphatemia resolves after the removal of the tumor and normalization FGF 23 levels.

With respect to treatment, it is generally recommended that patients with severe hypophosphatemia (< 1.0 mg/dL) should be treated to avoid potential serious clinical sequelae. For clinically asymptomatic patients who can tolerate oral intake, cow's milk is a good source of exogenous phosphorus (0.32 mmol per ml). Potassium and sodium phosphate oral preparations are also commercially available. In critically ill patients and those who are unable to tolerate oral intake, intravenous supplementation can be delivered at a rate of 0.08–0.16 mmol/kg over 6 h, depending on the severity of the deficit [84].

Case #5 Follow Up and Discussion

This patient has rhabdomyolysis from acute hypophosphatemia as a consequence of refeeding syndrome. The acute renal failure is due to myoglobinuria. The correct answer is (a).

Hyperphosphatemia

Case #6
A 44-year-old male is admitted for treatment of his recently diagnosed Burkitt'slymphoma. Prior to initiation of chemotherapy, the patient is started on hydration with 0.9 % NS at 150 ml/h and allopurinol 300 mg twice daily for prophylaxis against tumor lysis syndrome (TLS). His pretreatment laboratory tests report: creatinine 1.7 mg/dl, potassium 5.4 mEq/L, calcium 6.8 mg/dl, phosphorus 6.9 mg/dl, uric acid 12 mg/dl, and LDH 4000 U/L. Shortly after starting chemotherapy, the reports show a serum creatinine of 7.9 mg/dl, potassium 7 mEq/L, phosphorus 10 mg/dl, and calcium 4 mg/dl. He is now anuric and complaining for muscle twitching and circumoral numbness. The EKG shows changes consistent with hypocalcemia. How do you treat the hypocalcemia in this patient?

a. Intravenous calcium gluconate to normalize serum calcium
b. Start dialysis and then give IV calcium gluconate to normalize serum calcium
c. Intravenous calcium gluconate until the patient is not longer symptomatic and the EKG changes normalize

Hyperphosphatemia is defined as serum phosphate level > 5 mg/dL [96]. Renal insufficiency is the most common cause of hyperphosphatemia in the general population. In cancer patients, tumor lysis syndrome is the most common cause of hyperphosphatemia. When compared to mature lymphocytes, malignant lymphoblasts contain four times more intracellular phosphorus [97, 98]. The massive release of phosphorus into the systemic circulation, which typically occurs 24–48 h after administration of chemotherapy, can overwhelm the kidney's excretory ability. Serum phosphorus levels remain elevated because treatment with chemotherapy prevents reuptake of phosphorus by new tumor cells. When the solubility product of calcium and phosphorus in the serum exceeds 60 mg per square deciliter, calcium and phosphorus form precipitates, which can lead to metastatic calcifications in blood vessels, soft tissues, and the renal tubules[99]. In the kidneys, this may lead to intrarenal calcification, nephrocalcinosis, nephrolithiasis, and acute obstructive uropathy [96, 100]. Consequently, calcium infusions should be avoided in patients with hyperphosphatemia unless they are symptomatic from the hypocalcemia.

In addition to lowering oral and IV phosphorus intake, it has become common current clinical practice to use the non-calcium based phosphate binder sevelamer to lower serum phosphorus levels. The use of oral phosphate binders to lower serum phosphorus has been largely adapted from the literature on patients with end-stage renal disease on dialysis. Sevelamer works by binding phosphorus contained in food within the patient's gut. The maximal phosphate binding capacity occurs at a gastric

Table 7.1 Factitious electrolyte results and common causes

Factitious result	Disease entity/cause
Pseudophyperphosphatemia	IgG, IgM and IgA paraproteinemia
Pseudohypophosphatemia	IgG Paraproteinemia
Pseudohyponatremia	IgG, IgM, and IgA paraproteinemia, post intravenous gammaglobulin treatment
Pseudohypercalcemia	IgA, IgM paraproteinemia
Falsely low uric acid	IgM paraproteinemia
Falsely low albumin	IgM paraproteinemia,
Falsely low creatinine	IgG paraproteinemia
Falsely high creatinine	IgM paraproteinemia
Pseudohyperkalemia	Leukemias, Thrombocytosis, hemolysis
Pseudohypokalemia	Acute leukemias
Pseudohypobicarbonatemia	IgG, IgM paraproteinemia
Pseudohyperbicarbonatemia	IgM paraproteinemia
Pseudohypochloridemia	IgG paraproteinemia
Low urea levels	IgM paraproteinemia

pH of 7, and so its efficacy may be limited by concomitant use of proton pump inhibitors, which are frequently used in cancer patients undergoing chemotherapy [101]. There is only a single retrospective study on the use of sevelamer in pediatric cancer patients. In this retrospective study, only 13 children received sevelamer and only 5 of the 13 were known to be eating meals. Two of the 13 patients were on dialysis [102]. So, although sevelamer is routinely used to manage hyperphosphatemia in the setting of TLS, the clinical data to support its use is lacking, especially in those patients with no enteral nutrition. In addition to lowering GI absorption of phosphorus, infusion of hypertonic dextrose and insulin to shift phosphorus to IC space and can be used to manage hyperphosphatemia as well [103]. Continuous peritoneal dialysis, continuous veno-venous hemofiltration and hemodialysis have all been successfully employed in the treatment of TLS-associated acute hyperphosphatemia when there is concomitant impairment of renal function. [100]. The next chapter in this book deals in significant detail about TLS.

Of note, pseudohyperphosphatemia has been reported in patients with paraproteinemias and in patients receiving high dose of liposomal amphotericin B for treatment of severe fungal infections [96, 104]. The former appears to be the result of interference between the abnormal proteins and the laboratory assay. Table 7.1 summarizes the pseudo electrolyte disorders seen in cancer patients.

Case #6 Follow Up and Discussion
The coexistence of symptomatic hypocalcemia and hyperphosphatemia in an anuric patient requires careful management given the risk of calcium phosphate precipitation in the kidneys and soft tissues. Since the patient is symptomatic and the CaxPh product is < 60, IV calcium gluconate can be carefully administered until the patient's symptoms and EKG changes resolve, with care to not increase the product above 60. It is also appropriate to begin making arrangements for dialysis.

Potassium Disorders

Case #7
An elderly gentleman who has been managed expectantly for CLL presents for his routine clinic visit. He essentially has no complaints. Laboratory tests at the time of his office visit are remarkable for a WBC of 180,000/microL and the presence of anemia and mild thrombocytopenia. The serum K is 8.5 mEq/L. The patient is sent to the ER for further management of hyperkalemia. The repeat K is now 2.5 mEq/L. There are no EKG abnormalities and the physical exam and history remain unremarkable except for chronic lymphadenopathy.

What should be done next?

a. Admit for IV potassium repletion
b. Request a plasma K level
c. Give sodium polystyrene and place on a low K diet
d. Admit the patient to telemetry

Total body potassium content is about 50 mEq/kg (40 mEq/L for females), or roughly 3500 mEq in a 70 kg male. More than 95 % of potassium is contained in the intracellular space (muscle, RBCs, liver, bone); only 2–3 % is contained in the EC and plasma space. Intracellular potassium concentration is approximately 140 mEq/L compared with 4–5 mEq/L in the extracellular space.

Hyperkalemia

With this understanding of potassium distribution in the body, hyperkalemia can be approached in a very straightforward manner. Since the majority of total body potassium is contained in the IC space, intravascular hemolysis, or shifts of potassium from

the IC to EC space can produce clinically significant hyperkalemia. In cancer patients, leukocytosis (WBC > 100,000/m^3) and thrombocytosis (PLT > 800,000/m^3) can cause pseudohyperkalemia when potassium is released from cells after clotting has taken place in a blood vial [105]. These patients are asymptomatic with no typical EKG changes (peaked T's, prolonged QRS, absent P waves). To clarify the diagnosis, request a plasma sample for potassium measurement. Tumor lysis syndrome, rhabdomyolysis, thrombotic microangiopathy, and structural RBC abnormalities like hereditary spherocytosis, are all associated with intravascular hemolysis [106–110]. Exogenous potassium can be delivered via K+ containing IV fluids (Normosol®, lactated ringers), blood transfusions, and oral potassium supplements. Patients with upper GI bleeds or epistaxis can also absorb potassium as the blood is digested in the GI tract. Patients who have undergone ureteral diversions where the conduit is in contact with the jejunum can also present with hyperkalemia due to absorption of urinary potassium by the jejunum[111].

In the setting of ureteral or bladder neck obstruction due to malignancy, there is direct renal impairment of potassium elimination as well as abnormal secretion or subnormal effect of aldosterone, a hormone that is necessary for normal potassium handing in the distal tubule. A host of medications known to decrease aldosterone secretion or effect, and which can therefore cause hyperkalemia, includes heparin, cyclosporine, NSAIDs, spironolactone, trimethoprim, amiloride, ACE inhibitors, and angiotension receptor blockers [112–116].

Management of hyperkalemia involves a two pronged approach: (1) shift potassium back into the intracellular space and (2) remove potassium via the kidneys and GI tract. Beta agonists (nebulizer or IV), insulin (SQ or IV), and sodium bicarbonate (IV) acutely lower serum potassium within 30–60 min. These medications shift potassium to the IC space only transiently and their effect only persists for a few hours, so measures to excrete potassium also need to be employed. In a euvolemic or hypervolemic patient, furosemide and cation exchange resins (SPS, Kayexalate®) result in renal and GI elimination of potassium, respectively. Caution should be used when prescribing cation exchange resins given case reports of colonic necrosis associated with these agents [117]. Decreased colonic motility (from post-operative ileus or opiate administration) and concomitant sorbitol administration appear to be risk factors for colonic necrosis. In the volume contracted patients, intravenous NS increases distal sodium delivery and potassium secretion by the distal tubule. For patients with EKG abnormalities (peaked T's, prolonged QRS, absent P waves), IV calcium gluconate or calcium chloride is needed to stabilize the cardiac membranes. Dialysis may be appropriate for patients who have failed medical management; when hyperkalemia is severe; and in those situations where there is significant release of intracellular potassium (TLS, rhabdomyolysis).

Hypokalemia

Hypokalemia is one of the most common electrolyte abnormalities in hospitalized patients with an incidence of up to 20 % when it is defined as potassium level of < 3.6 mEq/L [118]. It is even more common in malignancy and occurs in approximately 75% of cancer patients at some point during their illness [119]. While most cases of hypokalemia represent true decrease in total body potassium content, spurious hypokalemia due to cellular uptake of potassium in vitro has been reported in rare patients with leukemia and markedly elevated white cell counts [120, 121].Although healthy individuals tend to tolerate mild hypokalemia, patients with ischemic or scarred myocardium may experience life-threatening arrhythmias. Severe hypokalemia of < 2.5 mEq/L may lead to rhabdomyolysis and concentrations of < 2.0 mEq/L are can cause paralysis and respiratory arrest [122].

Hypokalemia can be caused by poor intake, excessive losses, or intracellular shifts of potassium.Oral potassium intake below 1 g (25 mEq) per day may result in hypokalemia and cancer patients suffering from anorexia, nausea, or intestinal obstruction are at increased risk for this metabolic abnormality [118, 119]. Clinically significant potassium losses occur via the kidneys and the gastrointestinal tract, while losses via the skin are minimal except for extreme physical exertion. Several mechanisms are responsible for renal losses. Loop and thiazide diuretics are the most common causes of hypokalemia. Hypomagnesemia is another cause of renal potassium wasting. In cancer patients, cisplatin, aminoglycosides, amphotericin, pamidronate, and foscarnet can all cause hypomagnesemia-induced hypokalemia [123]. Proximal tubular dysfunction and Fanconi syndrome caused by ifosfamide or light chain toxicity from MM can also lead to renal potassium wasting. Albeit rare, there are case reports of patients with acute leukemia developing severe hypokalemia and kaliuresis. The postulated mechanism for this disorder is lysozyme-induced acute tubular injury [124]. A paraneoplastic syndrome of hypokalemia has been reported in small-cell tumors and in neuroendocrine neoplasms and carcinomas (renal cell tumors, colon cancers, and paragangliomas) that secrete ACTH. ACTH secretion leads to glucocorticoid excess and "spill over" effect on mineralocorticoid receptors in the distal nephron, resulting in enhanced potassium secretion [125]. Similar effects can be seen in patients on high dose steroid therapy and those receiving fludrocortisone, an oral mineralocorticoid, by its direct influence on mineralocorticoid receptors [122, 126].

Metabolic alkalosis caused by diuretic use, NGT drainage, and vomiting are also associated with hypokalemia. Chloride depletion from these same processes can also cause renal potassium wasting despite low serum potassium levels. The potassium content of stool losses is fairly small but when diarrhea develops, potassium wasting may substantial [118]. Large volume diarrhea in cancer patients can be related to chemotherapy, radiation enteritis, short gut syndrome, villous adenoma of the colon, vasoactive peptide secreting tumors, carcinoid, Zollinger–Ellison syndrome, graft versus host disease as well as infectious agents and antibiotic therapy[119].

Treatment of hypokalemia is the replacement of potassium deficit and the elimination of underlying causes of hypokalemia. Typically, every 0.3 mEq/L decline in serum potassium concentration corresponds to a 100 mEq total body deficit of potassium. For patients with significant deficits and those at risk for arrhythmias, hypokalemia needs to be corrected promptly and this can be done intravenously. However, since overcorrection is common and may lead to life-threatening hyperkalemia, and since oral preparations are generally well absorbed, this route may be more appropriate for milder cases of hypokalemia. In addition to supplementation, the use of potassium sparing diuretics may also be useful. For patients with concomitant, magnesium supplementation is essential for the correction of potassium deficit [118].

Case #7 Follow Up and Discussion
This is a case of spurious hyperkalemia and hypokalemia. For patients with very elevated WBCs, the cells can lyse in the test tube, producing hyperkalemia. Pseudohypokalemia can also occur since the cells are metabolically active and can take up potassium while in the test tube. A plasma sample should provide a more accurate read of the serum potassium. Choice (b) is correct. Table 7.1 within this chapter lists all noted pseudo-electrolyte disorders seen with cancer patients.

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Chapter 8
Tumor Lysis Syndrome

Scott J. Gilbert and Seth Wright

List of Abbreviations

TLS	Tumor lysis syndrome
AKI	Acute kidney injury
ALL	Acute lymphoblastic leukemia
CML	Chronic myelogenous leukemia
NHL	Non-Hodgkin's lymphoma
CLL	Chronic lymphocytic leukemia

> Autopsy showed the usual findings of chronic myeloid leukemia. The kidneys were of particular interest. Both contained multiple uric acid and urate calculi in the calyxes, and the upper portion of the ureter was packed with gravel. -Merrill and Jackson, 1943 [1].

In health, cell death is a coordinated, orderly apoptotic process with resulting products readily managed by the usual homeostatic mechanisms. In contrast, when the rate of cell death is massive and there is cell lysis rather than apoptosis, the sudden release of large quantities of intracellular elements can overwhelm the homeostatic mechanisms and can cause dramatic shifts in body chemistry. This can occur during the treatment of high-grade, large-volume tumors, but can also spontaneously in the case of tumors with high intrinsic growth rates as the malignant cells proliferate, overgrow, and necrose [2]. The constellation of chemical and clinical abnormalities caused by the release of intracellular content from dying tumor cells is referred to as the tumor lysis syndrome (TLS). The major intracellular elements are potassium (leading to hyperkalemia), phosphate (leading to hyperphosphatemia and hypocalcemia), and nucleic acids, which are metabolized to uric acid and other products. These products of nucleic acid metabolism can form crystals in the urine and cause

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obstruction of urinary flow, one of the leading causes of acute kidney injury (AKI). As this obstruction may occur as radiolucent urate sludge in the tubules, it may not be apparent on radiologic images. Tumor cell death is also associated with the release of cytokines that may be of clinical import [3], but these are not typically considered part of the syndrome and will not be discussed further here.

History and Evolving Understanding

The first mention of treatment-related TLS was made nearly a century ago in a report of obstruction from uric acid crystals after radiotherapy of leukemia [4]. The risk of hyperuricemia, including kidney failure from urinary obstruction, quickly became more generally appreciated [5]. As treatments became more effective and measurements more precise, other metabolic complications were reported, including hyperkalemia and hyperphosphatemia (with associated hypocalcemia) soon after chemotherapy for Burkitt lymphoma [6, 7]. The observation that TLS can arise spontaneously in the absence of chemotherapy due to high cell turnover was later made in lymphoma [2]. That this syndrome was originally recognized in high-grade hematologic malignancies is presumably related to the high tumor burden and the rapid response to treatment in these diseases. However, in the last decades it has become apparent that TLS can appear in solid tumors as well, or after treatments other than standard chemotherapy.

Definition and Framework

Since the rate of cell death can be on a continuum from trivial to catastrophic, the exact point at which abnormalities reach the point of "TLS" is somewhat arbitrary. In addition, the clinical impact is affected by the body's fluctuating ability to manage the influx of intracellular products, since hemodynamic factors and kidney function can change during the course of illness. Nevertheless, in principle, TLS can be divided into three broad categories:

1. *No syndrome*, indicating that cell lysis occurs with only minor changes in body chemistries;
2. *Laboratory TLS*, where laboratory values are substantially abnormal but have not yet induced clinical manifestations; or
3. *Clinical TLS*, where disturbances reach a level that has clinical consequence or requires urgent intervention. This is generally a subset of the laboratory TLS category.

Several systems to formally define these categories have been proposed, [8] but the current classification for research and clinical purposes was established by Cairo and Bishop in 2004, [9] with minor modifications by later authors. In this classification system, laboratory values are assessed on days -3 to $+7$ relative to treatment

(Table 8.1). This system scores the severity of clinical symptoms and signs, for a grade of 0–5. Later, authors have suggested minor changes including the inclusion of symptomatic hypocalcemia as an additional criterion for clinical TLS [3], and the elimination of stages 0 (no disease) and 5 (death) [10].

Clinical Presentation

TLS is most commonly seen after directed therapy has caused rapid tumor cell death, but can also occur spontaneously. High-grade, aggressive tumors like Burkitt lymphoma or T-cell acute lymphoblastic leukemia (ALL) represent the majority of cases, but TLS may complicate other tumor types associated with large tumor burdens, rapid proliferation rates, or high sensitivity to chemotherapy. The first signs and symptoms may appear within 24–72 h of initiation of chemotherapy or embolization, but a more indolent course has been observed over weeks to months with spontaneous development of TLS.

Case #1
A 42-year-old man presented with 3 months of lethargy, malaise, intermittent low-grade fevers, and a 10-kg weight loss. He was actively treated with hydrochlorothiazide for hypertension diagnosed 4 years earlier. One week prior to presentation, he noted painful swelling in his neck, axillae, and groin, and 2 days earlier developed palpitations, restless legs, and paresthesias in his fingertips. On examination, his temperature was 38.7 °, heart rate 92 bpm, and blood pressure 96/62 mmHg. His conjunctivae were pale and mucous membranes dry. He had tender lymphadenopathy in both axillae, in the groin, and on neck exam in the posterior cervical chain. His heart rate was regular with frequent premature ventricular contractions. His lungs were clear. On abdominal examination, his liver span was slightly increased and tender, and a spleen tip was palpable at the level of the umbilicus. Extremities revealed 2+ dependent edema, scattered petechiae, and 2+ distal pulses. Cranial nerves were intact, but a Chvostek sign was noted upon tapping the left facial nerve. Laboratory testing identified potassium 6.6 mEq/L, bicarbonate 16 mEq/L, anion gap 22, creatinine 5.8 mg/dL, albumin 3.1 mg/dL, calcium 5.9 mg/dL, phosphate 18.7 mg/dL, and uric acid 21.3 mg/dL. Blood counts showed a white blood count (WBC) of 125 K with abundant blasts, hemoglobin 7.2 mg/dL, and platelets 17 K. Urinalysis demonstrated a specific gravity of 1.012, pH 5.5, 1+ protein and 2+ blood, and sediment with degenerating tubular cells and amorphous phosphate crystals. Because of progressive kidney failure, hyperkalemia, and dropping urine output in the setting of TLS, urgent dialysis was initiated. Computed tomography of the chest, abdomen, and pelvis identified

diffuse lymphadenopathy, and bone marrow biopsy confirmed the diagnosis of T-cell ALL.

Which of the following tumor types is least commonly associated with TLS?

a. Burkitt's lymphoma
b. T cell ALL
c. Non-Hodgkin lymphoma (NHL)
d. Breast cancer with high tumor load
e. Chronic myelogenous leukemia (CML)

Epidemiology and Risk Factors

As mentioned earlier, the majority of the reported cases have been observed in hematologic malignancies [11], although the incidence varies widely by tumor type. A series of 102 patients with NHL showed an overall incidence of nearly 50 % by laboratory values, although only 6 % met clinical criteria [8]. In an observational study of patients with acute myeloid leukemia (AML), 17 % had TLS (12 % by laboratory values alone and 5 % by clinical criteria as well) [12]. An incidence of 46 % has been reported in chronic lymphocytic leukemia (CLL) [13].

It has also become apparent that tumor lysis can occur in many situations other than hematologic malignancies being treated with standard chemotherapy. Tumor lysis has been reported in the treatment of solid cancers such as breast [14], melanoma [15], gallbladder [16], lung [17], liver [18], gastric or gastrointestinal [19, 20], pancreatic [21], yolk sac [22], prostate [23], colorectal [24], testicular [25], medulloblastoma [26], and sarcoma [27]; although the incidence with these tumors remains unknown due to the limits of case reporting. In addition, it has become apparent that the trigger need not be standard cytotoxic therapy, with TLS reported after treatment with steroids, biological agents such as rituximab or interferon [14, 28–31], embolization [18, 32], surgery/anesthesia [33, 34], and even vaccination [35]. A tumor lysis-like condition has been reported during the use of granulocyte colony-stimulating factor in the correction of leucopenia [36]. Clearly, it is important to be cognizant of this syndrome outside of the more traditional framework of hematologic malignancy.

Case #1 Follow-up and Discussion

The patient presented above has TLS. As discussed, all hematologic malignancies have been associated with TLS. Most of the cases of solid tumor-associated lysis occur in the setting of high tumor burden, and have been isolated case reports. Indolent cancers like CML rarely cause TLS.

Table 8.1 Criteria for laboratory and clinical TLS, modified from Cairo and Bishop 2004. (Modified Cairo-Bishop criteria (2004) [9], with modifications as suggested by Howard 2011 [3], Tosi 2008 [10], or Cairo 2010 [38] indicated in italics)

Laboratory TLS: two or more of (within −3 to +7 days relative to treatment)	Clinical symptoms (any of)	Clinical I	Clinical II	Clinical III	Clinical IV
Uric acid > 8 mg/dL (476 μmol/L) in adults, > age- normal in children Potassium > 6 mmol/L	Creatinine [9] *or* estimated kidney function [10][a]	< 1.5 × ULN, 30–45 ml/min	1.5–3xULN, 10–30 ml/min	3–6xULN, 10–20 ml/min	> 6 x ULN, < 10 ml/min or kidney replacement therapy
Phosphorous > 4.5 mg/dL (1.5 mmol/L) (adults) or > 6.5 mg/dl (2.1 mmol/L) (children)	Cardiac	Arrhythmia, no intervention	Nonurgent medical treatment	Symptomatic; incompletely controlled medically, or needing device (e.g., defibrillator)	Life-threatening with shock, syncope, hypotension, or CHF
Calcium: < 7 mg/dL, 1.75 mmol/L (corrected for albumin), or ionized < 1.12 mmol/L; *omitted by most recent schema* [38]	Neuromuscular	*Any symptomatic hypocalcemia* [3]*; grade not specified*	Single brief generalized seizure, rare focal motor seizures, or seizures well-controlled medically	Seizure with altered consciousness; generalized seizures despite medication	Repetitive seizures despite medication (e.g., status epilepticus)
Any of the above with > 25 % increase from recent baseline (or decrease for calcium) [9, 10, 38]; *others specifically exclude this Criterion* [3]					

CHF congestive heart failure, *ULN* upper limit of normal

[a]By an estimating equation (for adults, CKD-EPI, MDRD, or Cockcroft–Gault; for children, Schwarz)

Patient Risk Factors

Certain patient characteristics have been associated with an increased likelihood of developing TLS. Intuitively, the risk would be expected to be highest when tumor burden is large and in those diseases highly responsive to treatment. In a series of 328 children with ALL, TLS was noted in 74 (23 %). Factors predictive of TLS on a multiple regression analysis included age ≥ 10 years (OR 4.5), the presence of splenomegaly (OR 3.3) or a mediastinal mass (OR 12.2), and WBC $\geq 20 \times 10^9$/L (OR 4.7) [37]. Other authors studying AML have reported an association with high LDH, WBC count over 25×10^9/L, as well as an elevated creatinine and uric acid [12]. The usefulness of these predictors has generally not been studied in validation cohorts or in patients with malignancies other than those from which the predictors were derived. Nevertheless, there have been several risk stratification algorithms proposed [38−40] which involve the general consideration of laboratory values, tumor type, and preexisting chronic kidney disease.

As previously mentioned, the presentation of TLS may occur with either abnormal laboratory parameters or the clinical manifestations of these disturbances. The *laboratory presentation* results from the release of intracellular molecules into the plasma, or the secondary effect of these chemicals on serum calcium levels. The abnormalities of the laboratory presentation according to the Cairo–Bishop criteria are listed in Table 8.1, and include the presence of two or more of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Nucleic acids, potassium, and phosphates are in high concentration in the intracellular environment, and released into the plasma under circumstances of rapid and extensive cell death. Hypocalcemia is a secondary effect of released phosphates complexing with plasma calcium and depositing in soft tissues and interstitial spaces. This typically occurs when the calcium-phosphate product reaches levels greater than $60\,mg^2/dl^2$.

The *clinical presentation* occurs when symptoms and signs develop as a result of these changes. Generalized symptoms of anorexia, nausea, vomiting, diarrhea, and lethargy are common. Cardiac complications, including cardiac dysrhythmias, heart failure, syncope, and possible sudden death, may reflect hyperkalemia, hypocalcemia, and deposition of calcium-phosphate in the myocardium, disrupting contractility and electrical conduction. Neuromuscular effects include muscle spasms, tetany, and seizures.

The manifestations of TLS in the kidney include AKI, hematuria, oliguria, flank pain, and nephrolithiasis. The development of AKI is related to a variety of factors, including renal vasoconstriction, disrupted autoregulation, reduced renal blood flow, inflammation, tubular epithelial cell injury, and intra tubular deposition and obstruction by crystals. Uric acid and calcium-phosphate deposition within the renal pelvis or as ureteral stones may be responsible for many of these clinical manifestations. The urinalysis often demonstrates uric acid crystals or amorphous urate in acidic urine. The kidney pathology includes calcium-phosphate crystals in the interstitium (Fig. 8.1a) and uric acid crystals resulting in tubular obstruction (Fig. 8.1b). Xanthine is another poorly soluble metabolite of purine metabolism that can deposit in tissues.

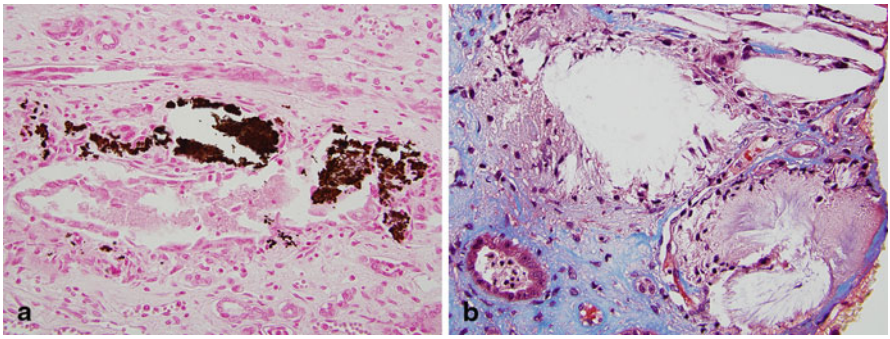

Fig. 8.1 Panel **a** shows cortical tubules with injury and calcium-phosphate deposition in the lumen, epithelium, and interstitium. Von Kossa stain demonstrates-phosphate (but not oxalate) deposition (original magnification 40 ×). Panel **b** shows urate deposits in renal medulla (Masson Trichrome, original magnification 40 ×)

Outcomes

The development of TLS is associated with a series of clinical complications, including prolonged hospitalization, increased morbidity, and reduced survival. In a retrospective series of 772 patients with AML, clinical TLS (but not laboratory TLS) was associated with a 79 % risk of death (30 of 38 patients) versus 23 % in those who failed to meet criteria. This mortality included kidney failure, arrhythmias, and coma felt to be directly attributable to TLS [12].

Though not specifically addressing tumor lysis as a cause, the development of AKI complicating treatment of hematologic malignancies (excluding Hodgkin's disease) has been identified as a major factor in prolonged hospitalization and higher inpatient medical costs. Analysis of data on over 400,000 patients from the Health Care Utilization Project revealed patients who developed AKI requiring dialysis, developed AKI without dialysis, and had no kidney complications has mean hospital stays of 17.6, 12.2, and 7.4 days, with hospitalization costs (in 2006 dollars) of $ 44,619, 25,638, and 13,947, respectively [41].

In another European analysis of 755 patients with ALL, AML, or NHL, 27.8 % met criteria of TLS. Patients requiring dialysis for TLS had hospitalization costs 26-fold greater than patients who developed hyperuricemia without fulfilling criteria for TLS or requiring dialysis. Death was attributable to TLS in 15 (2 %) patients [42].

Pathophysiology and Pathology

As noted, the laboratory and clinical manifestations of TLS result from the release of intracellular contents such as nucleic acids, potassium, phosphates, and other chemicals after extensive tumor lysis which results in a cascade of pathologic and

pathophysiologic processes. The intracellular concentration of potassium is approximately 150 mEq/L, and cellular damage results in the spillage of this potassium into the extracellular space and plasma. This hyperkalemia may disrupt the Nernst potential governing cellular depolarization, opening voltage-gated sodium channels before inactivating the same channels. This action impairs neuromuscular, cardiac, and gastrointestinal function, thereby affecting cardiac conduction and inciting ventricular arrhythmias and asystole.

Phosphate is the most abundant intracellular anion, found primarily as adenosine phosphates (AMP, ADP, and ATP) and in DNA and RNA. Furthermore, tumor cells may have a phosphate content greater than four times that of normal cells [43]. The clinical manifestations of an extracellular phosphate load induced by extensive cell death are typically kept in check by the high capacity of the kidney to excrete phosphate. However, in the setting of reduced kidney function or simultaneous kidney injury as occurs in TLS, phosphate accumulation results in hyperphosphatemia. The direct clinical manifestations of hyperphosphatemia are limited, but extracellular phosphate complexes with ionized plasma calcium and deposits as calcium-phosphate crystals in the kidneys, vasculature, and soft tissues. This results in a fall in plasma concentrations of free calcium and clinical hypocalcemia. Since calcium inhibits sodium channels and depolarization of nerves and muscles, acute hypocalcemia lowers the threshold for depolarization and clinically manifests as tetany, seizures, hyperreflexia, cardiac arrhythmias, and possibly death. Tetany is neuromuscular irritability and hyperexcitability, with symptoms ranging from perioral numbness and paresthesias to carpopedal spasm and laryngospasm. Trousseau sign (carpopedal spasm induced by inflation of a sphygmomanometer above systolic blood pressure for 3 min) and Chvostek sign (contraction of the ipsilateral facial muscles elicited by tapping the facial nerve just anterior to the ear) are two of the more common features of tetany in hypocalcemia. The cardiac complications of hypocalcemia include impaired inotropy leading to reversible heart failure, and electrophysiologic derangements from prolonged QT interval to heart block and ventricular arrhythmias. Other manifestations of hypocalcemia in TLS include psychiatric lability, mood instability, and papilledema.

The effects of calcium and phosphate deposition in the kidney induce a variety of insults. Calcium-phosphate crystals that deposit in tubular lumina can result in urinary obstruction. In addition, these crystals appear within tubular epithelial cells where they exert direct tubular toxicity and in the interstitium where they incite an inflammatory response. This is evident on kidney biopsy that demonstrates localization of phosphate using von Kossa stain in the lumen of the distal tubule, with lesser deposits in the tubular interstitium and in the epithelial cells (Fig. 8.1a). Tubular atrophy, tubular necrosis, and nephrocalcinosis are consequences of calcium-phosphate deposition. In the current era of uric acid-lowering therapy, calcium-phosphate deposition presumably represents an increasingly important contributor to kidney damage.

Nucleic acids are also released following cellular destruction. Purines undergo a series of reactions resulting in their degradation, with guanosine metabolized by purine nucleoside phosphorylase to guanine, and then by guanine deaminase into xanthine (Fig. 8.2). Adenosine is metabolized by adenosine deaminase into inosine,

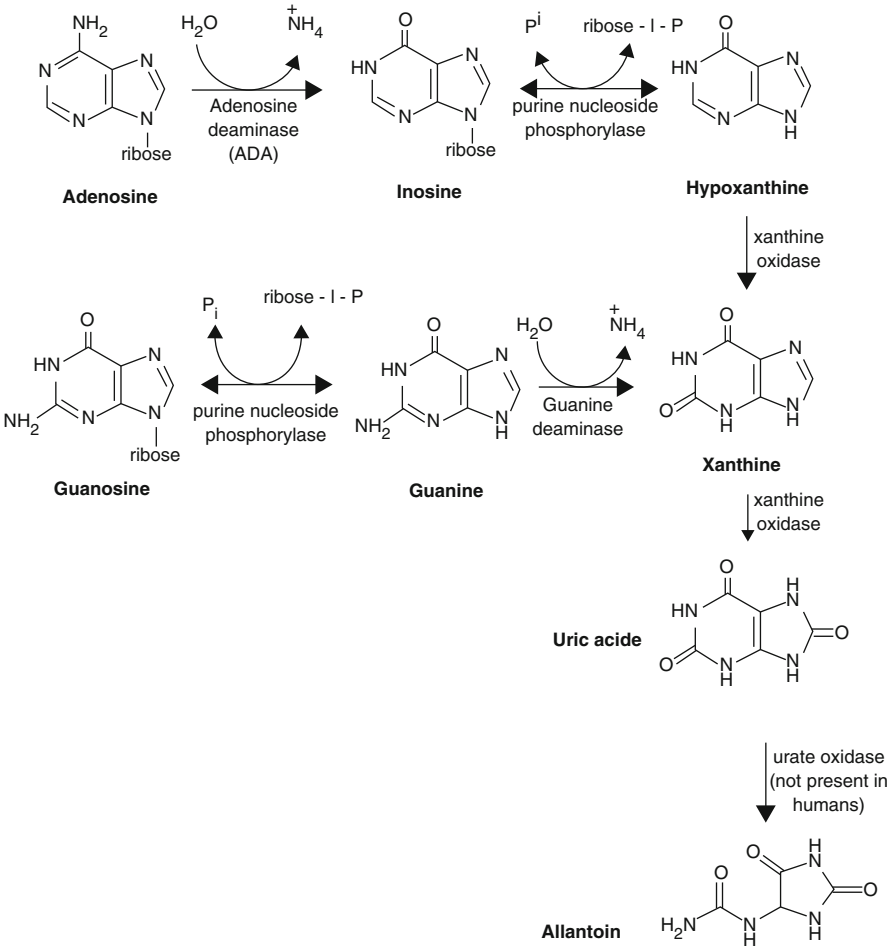

Fig. 8.2 Purine metabolism

and then purine nucleoside phosphorylase into hypoxanthine. Hypoxanthine is first converted to xanthine by xanthine oxidase, before xanthine is metabolized into uric acid. Uric acid is a weak acid with a pK_a of 5.75. This means that at a physiologic pH of 7.4, 98 % of uric acid is in its ionized form of urate. In the acidic environment of the distal tubule where the pH falls below 5.0, equilibrium favors the less-soluble protonated form of uric acid that precipitates as crystals. The large load of filtered urate in TLS along with its rising concentration along the length of the tubule results in tubular precipitation in the increasingly acidic environment of the distal tubule. This leads to obstruction of tubules, collecting ducts, and even pelvises and ureters.

The precipitation of uric acid in the tubules is enhanced by the presence of a calcium-phosphate crystal nidus, and conversely, calcium-phosphate precipitation

is enhanced by the presence of uric acid crystals. Together, high concentrations of calcium-phosphate and uric acid potentiate the risk of AKI.

Tubular obstruction from crystal deposition induces a cascade of processes that result in AKI. Increased tubular pressure raises intrarenal pressure and compresses venous channels within the kidney. The increase in vascular resistance reduces renal blood flow. Together, high tubular pressures and reduced renal blood flow lower glomerular filtration rate.

Case #2

A 14-year-old girl presented to her pediatrician with 1 week of abdominal bloating, nausea, vomiting, and malaise. She had previously been well, but the distension occurred rapidly and resulted in extreme discomfort. On examination, her temperature was 38.2 C, heart rate 110 bpm, and blood pressure 86/68 mmHg. Her oropharynx was clear and no cervical lymphadenopathy was present. Her heart was regular, and her lungs were clear. Her abdomen was distended and diffusely tender, with a palpable fluid wave. An epigastric mass was appreciated. Axillary and femoral lymphadenopathy was absent. Extremities revealed 2+ dependent edema. Laboratory testing showed potassium of 3.1 mEq/L, bicarbonate 22 mEq/L, creatinine 0.8 mg/dL, eGFR 111 ml/min/1.73 m^2 by the CKD-EPI equation, albumin 4.2 mg/dL, calcium 8.6 mg/dL, phosphate 1.2 mg/dL, and LDH 850 U/L. Blood counts showed a WBC of 125 K, hemoglobin 13.8 mg/dL, and platelets 229 K. Computed tomography of the abdomen demonstrated ascites and a 14-cm mass compressing the antrum of the stomach. Biopsy of the abdominal mass showed monomorphic, medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm. Cell surface expression of CD19, CD20, CD22, CD79a, CD10, HLA-DR, and CD43 confirmed the diagnosis of Burkitt lymphoma. Treatment with EPOCH with rituximab was considered, but prophylaxis for TLS was first felt necessary.

What agent would you recommend for prevention of TLS?

a. Volume expansion with bicarbonate based fluids
b. N-acetyl-L-cysteine
c. Recombinant urate oxidase
d. Allopurinol

Prevention and Treatment

Although guidelines for the management of TLS exist, they are not grounded on large quantities of clinical trial data given the relatively rarity of the condition [39]. In general, the therapies for TLS are more effective when used for prevention, in

part because kidney failure may not be readily reversed. Therefore, the mainstay is recognizing the possibility of tumor lysis and implementing an early and liberal administration of inexpensive preventative measures. There are additional therapies, either given preventatively to patients at particular risk or therapeutically as warranted by developments in the clinical course.

There are three major therapies available for prevention or treatment of TLS: volume expansion (with or without forced diuresis), allopurinol, and recombinant urate oxidase.

Volume Expansion

Hypovolemia and reduced kidney function are risk factors for developing TLS, and the early and copious administration of intravenous fluid is a mainstay of TLS treatment. The goal is not so much volume expansion per se, but the optimization of kidney function and the initiation of a brisk diuresis. A high urinary flow rate causes the daily burden of uric acid, phosphate, and other metabolites to be less concentrated in the urine and therefore less likely to precipitate into obstructing crystals. In addition, uric acid handling by the proximal tubule is coupled to sodium transport, such that volume contraction and the accompanying sodium avidity increase urate reabsorption and diminish its urinary clearance. Conversely, circumstances of adequate volume expansion and reduced tubular sodium reabsorption are associated with reduced urate reabsorption and enhanced excretion.

In general, aggressive intravenous fluid resuscitation is indicated for nearly everyone in whom tumor lysis is considered. By clinical practice, the administered fluid tends to be dextrose/quarter-normal saline in children [44], and isotonic or dextrose/half-normal saline in adults, but can be tailored to the individual patient. Assuming that there is no contraindication such as heart failure, the rate of fluid administration can be quite high: 2–3 L/day/m^2 BSA [40] starting 2 days before and lasting until 3 days after chemotherapy [45].

Though it has not been studied in a controlled manner, diuretics have been used on a theoretical basis to maintain urinary flow at a rate of 100 ml/m^2 BSA/h [3, 9]. It is important to appreciate that the goal is high urine flow, not actual negative fluid balance. Diuretics should only be considered in adequately volume loaded patients who are simultaneously receiving intravenous fluids.

Because of the increased solubility of uric acid in alkaline urine, prior practice was to routinely administer sodium bicarbonate with the goal of raising urine pH, increasing urate solubility, and reducing uric acid precipitation. However, concerns were later raised that this may *reduce* solubility of calcium-phosphate complexes, which can also be a cause of kidney failure with tumor lysis [46]. In addition, hypocalcemia is common in tumor lysis, and alkalinization of the serum may reduce the ionized fraction of calcium and worsen the symptoms of hypocalcemia [47]. More recent guidelines, therefore, no longer recommend routine prophylactic alkalinization in the treatment of TLS [39]. Of course, this does not preclude the use of alkalinization

when specifically indicated for other clinical reasons, for example, in the urgent treatment of hyperkalemia or metabolic acidosis, the latter occurring in the setting of severe TLS in patients with evolving AKI .

Allopurinol

Allopurinol is an inhibitor of xanthine oxidase that reduces the conversion of xanthine to uric acid (see Fig. 8.2). When given intravenously as prophylaxis, it has prevented an increase in uric acid levels in most patients at risk for TLS [48]. The doses used in children and adults are weight-based up to a maximum of 600 mg IV or 800 mg orally per day, given in divided doses. Dose reduction is required in the presence of kidney disease. Therapy is started 1–2 days before chemotherapy and is continued until 3–7 days after its conclusion [39]. Though there is no specific advantage to the intravenous route of administration, it allows more reliable dose delivery than the oral form in patients with gastrointestinal issues related to disease or treatment.

There is extensive experience with allopurinol, and it is recommended for use in patients at intermediate risk of tumor lysis [40]. However, allopurinol has the disadvantage that it cannot affect uric acid that has already been generated. It may also lead to an increase in uric acid precursors such as xanthine, which themselves may precipitate in the kidney [49]. In addition, allopurinol has multiple drug interactions and may require dose adjustments or avoidance with certain chemotherapeutic agents or other medications.

Rasburicase

The rapid degradation of uric acid into highly soluble allantoin is possible enzymatically by urate oxidase (see Fig. 8.2), but this enzyme is absent in primates. The use of nonrecombinant urate oxidase (uricosyme) was an early approach to address this deficiency [50]. While effective in lowering uric acid levels, it had an incidence of severe allergic reactions in nearly 5 % of patients [51]. In 2001, a recombinant form of urate oxidase, rasburicase, was reported as highly effective in controlling uric acid levels when compared to allopurinol, with a low rate of adverse events [52]. It is extremely effective with nearly all patients reaching normal or low levels of uric acid [53, 54]. In addition, unlike allopurinol, it can eliminate pre-formed uric acid rather than simply prevent more formation. Rasburicase was initially FDA-approved in the USA in 2005 for the treatment and prevention of tumor lysis-related hyperuricemia in children [55], and in adults in 2009.

Since its initial introduction, there has been some evolution in its role. After additional reporting, it is still considered a safe therapy with relatively few adverse reactions. However, its action involves the production of hydrogen peroxide, and in patients with G6PD deficiency can be associated with the development of methemoglobinemia and hemolytic anemia; it is contraindicated in patients with

this condition [56, 57]. There are also reports of the development of anti-rasburicase antibodies, though the clinical significance of this is unclear with no hypersensitivity reactions during the initial course of therapy [53, 58]. Meta-analyses of the adult and pediatric literature have not shown definite improvement in kidney failure or death outcomes [54, 59], but given the dramatic metabolic improvements, rasburicase has established itself in guidelines and clinical practices.

The major limitation to the use of rasburicase is its cost. The label recommends a dose of 0.2 mg/kg for up to 5 days, with costs in the many thousands of dollars [42]. This makes it potentially prohibitive for routine use. In a European cost-effectiveness analysis of ALL/NHL/AML patients with an overall incidence of TLS around 5 %, rasburicase *treatment* of established tumor lysis was cost-saving in most cases [42]. In children, *preventive* use of rasburicase was highly cost effective with an estimated incremental cost of 445–3054 € per life-year saved. In adults, the incremental cost per life-years saved by preventive use was 41,383 € in NHL, 32,126 € in ALL, and close to 100,000 € in AML, due to the limited survival of these patients. Others have explored whether reduced dosing might be effective. For example, a dose of 0.15 mg/kg/day [53] or a 3 mg fixed dose [60−62] in children has been tested. Others have proposed a 3-day course instead of 5 days (with follow-up allopurinol), or single-dose protocols (repeated as necessary for uric acid > 7.5 mg/dL) for adults using 6 mg [63] or 0.15 mg/kg doses [55]. In a single-dose randomized trial, only 6 of 40 (15 %) patients in the single-dose arm required a second dose. Outcomes were similar to the daily dosing arm, but with fewer side effects. Patel has pointed out that a 1-day course of rasburicase might even be less expensive than a multiple-day course of intravenous allopurinol in patients unable to take oral medication, once the costs of administration are taken into account [64]. In summary, it appears that rasburicase is highly effective, but the minimum effective dose to achieve adequate results is still an area of exploration.

Case #2 Follow up and Discussion

The 14-year-old girl is at high risk of TLS. Volume expansion with normal saline to maintain a urine flow rate of 2–3 L/day would be beneficial in preventing the syndrome. Diuretics should only be considered in adequately volume expanded patients who are simultaneously receiving intravenous fluids. Bicarbonate-based fluids reduce the solubility of calcium-phosphate complexes, which can also be a cause of kidney failure with tumor lysis [46]. In addition, hypocalcemia is common in tumor lysis, and alkalinization of the serum may reduce the ionized fraction of calcium and worsen the symptoms of hypocalcemia [47]. More recent guidelines, therefore, no longer recommend routine prophylactic alkalinization in the treatment of TLS [39]. In children, preventive use of rasburicase was highly cost-effective with an estimated incremental cost of 445–3054 € per life-year saved. It is extremely effective with nearly all patients reaching normal or low levels of uric acid [53, 54], making this the best of the options given.

Medical Management of Electrolyte Abnormalities

In general, the management of hyperkalemia related to TLS is not different from the management of hyperkalemia from other causes. Hypocalcemia should be treated if symptomatic with intravenous calcium gluconate. However, if the patient is asymptomatic, supplementation should generally be avoided as hyperphosphatemia may lead the administered calcium to simply complex and precipitate without benefit (but some risk) to the patient. Hyperphosphatemia, if severe, can be treated with oral phosphate binders such as a short course of aluminum hydroxide, though there are no studies testing its specific role in TLS [3]. For the reason just described, calcium-based phosphate binders should generally be avoided.

Kidney Replacement Therapy

The use of prophylactic kidney replacement therapy has been explored in patients at particularly high risk, using continuous venovenous hemofiltration [65]. This prophylactic approach was associated with improved control of laboratory values, as expected. However, in general, kidney replacement is reserved for situations where it is clinically required for treatment rather than as prophylaxis. There is no specific evidence to favor continuous versus intermittent kidney replacement therapy, though it is worth noting that the continuous therapies tend to have a more effective clearance of phosphate if that is a particular clinical concern.

General Strategy

A strategy for identifying prophylaxis for patients at different risk for tumor lysis has been outlined in a consensus guideline by Cairo et al., among others [38]. Risk is stratified into low ($< 1\,\%$), intermediate (1–5 %), and high ($> 5\,\%$) on the basis of tumor type, lab values, and patient characteristics. The algorithm is complex, but overall recommends the use of monitoring and intravenous fluids in all patients, with low-risk patients considered for prophylactic allopurinol; intermediate-risk patients treated with prophylactic allopurinol; and high-risk patients treated with prophylactic rasburicase [38]. An example from the consensus guidelines for specific diseases is reproduced in Table 8.2, with more detail available in the full guidelines. A closely related schema has been proposed by Tosi et al. (2008) [10].

Table 8.2 Consensus guidelines for treatment and prevention of TLS. (Reproduced from Cairo 2010) [38]

Low-risk disease	Intermediate-risk disease	High-risk disease
ST[a]	N/A	N/A
MM	N/A	N/A
CML	N/A	N/A
Indolent NHL	N/A	N/A
HL	N/A	N/A
CLL[b]	N/A	N/A
AML and WBC $< 25 \times 10^9$/L and LDH $< 2 \times$ ULN	AML with WBC 25–100 $\times 10^9$/L AML with WBC 25 $\times 10^9$/L and LDH $\geq 2 \times$ ULN	AML and WBC $\geq 100 \times 10^9$/L
Adult intermediate grade NHL and LDH $< 2 \times$ ULN	Adult intermediate grade NHL and LDH $\geq 2 \times$ ULN	N/A
Adult ALCL	Childhood ALCL stage III/IV	N/A
N/A	Childhood intermediate grade NHL stage III/IV with LDH $< 2 \times$ ULN	N/A
N/A	ALL and WBC $< 100 \times 10^9$/L and LDH $< 2 \times$ ULN	ALL and WBC $\geq 100 \times 10^9$/L and/or LDH $\geq 2 \times$ ULN
N/A	BL and LDH $< 2 \times$ ULN	BL stage III/IV and/or LDH $\geq 2 \times$ ULN
N/A	LL stage I/II and LDH $< 2 \times$ ULN	LL stage III/IV and/or LDH $\geq 2 \times$ ULN
N/A	N/A	IRD with reduced GFR and/or kidney involvement IRD with uric acid, potassium and/or phosphate ULN
Prophylaxis recommendations		
Monitoring	Monitoring	Monitoring
Hydration	Hydration	Hydration
± Allopurinol	Allopurinol	Rasburicase[c]

ST solid tumors, *MM* multiple myeloma, *CML* chronic myeloid leukemia, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *CLL* chronic lymphoid leukemia, *AML* acute myeloid leukemia, *WBC* white blood cell count, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *ALCL* anaplastic large cell lymphoma, *N/A* not applicable, *ALL* acute lymphoblastic leukemia, *BL* Burkitt lymphoma/leukemia, *LL* lymphoblastic lymphoma, *IRD* intermediate risk disease

[a]Rare solid tumors, such as neuroblastoma, germ cell tumors, and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD

[b]CLL treated with fludarabine, rituximab, and/or those with high WBC (‡50 · 109/l), should be classified as IRD

[c]Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol

Summary

TLS is a potentially serious complication during the treatment of tumors, particularly in patients with high grade cancer and large tumor burden. Practitioners need to be aware that it can arise during treatment of nearly any tumor, and though usually related to treatment, can arise spontaneously. Prophylactic measures include administration of intravenous fluids, with escalating therapies to lower uric acid guided by clinical risk. Though evidence is limited, there are multiple guidelines and scoring systems to assist practitioners in directing therapy.

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Chapter 9
Surgical and Medical Options in the Management of Renal Cell Carcinoma

Simpa S. Salami, Manish A. Vira and Thomas P. Bradley

List of Abbreviations

AS	Active Surveillance
AUA	American Urological Association
BHD	Birt–Hogg–Dube
CKD	Chronic kidney disease
CR	Complete response
CT	Computed tomography
DFS	Disease-free survival
EORTC	European Organization for Research and Treatment of Cancer
ESKD	End-stage kidney disease
FGFR	Fibroblast growth factor receptor
GFR	Glomerular filtration rate
HLRCC	Hereditary Leiomyomatosis Renal Cell Cancer
HIF	Hypoxia inducible factor
IV	Intravenous
KPS	Karnofsky performance score

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MRI	Magnetic resonance imaging
MPA	Medroxyprogesterone
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NSS	Nephron sparing surgery
OS	Overall survival
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PN	Partial nephrectomy
RCC	Renal cell cancer
RFA	Radiofrequency ablation
RN	Radical Nephrectomy
TGF	Transforming growth factor
TKI	Tyrosine kinase inhibitors
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	von Hippel–Lindau

Case #1

AA is a 47-year-old male presented to the emergency department with a 1-day history of gross hematuria. Upon presentation, his vital signs were stable and the remainder of his exam was unremarkable. In the emergency department, a complete blood count revealed normal hematocrit and serum creatinine of 1.04 mg/dL. He underwent an MRI of the abdomen with and without IV contrast. Imaging revealed an 8 cm heterogeneous mass in the mid pole of the right kidney with mixed signal intensity but definite areas of enhancement (Fig. 9.1). Metastatic workup revealed no evidence of distant metastasis. His past medical history was significant for hypertension, hyperlipidemia, and non-insulin dependent diabetes mellitus (currently on metformin). Given his medical comorbidities and risk of future renal insufficiency, nephron-sparing surgery was recommended. He underwent a robotic-assisted laparoscopic partial nephrectomy. The surgery was uncomplicated, and the warm ischemia time during resection (minutes that the clamp was occluding arterial inflow) was 23 min. Upon resection, pathology revealed a clear cell renal cell carcinoma (RCC), Fuhrman grade 3, confined to the kidney (T2aNxMx). Postoperatively, creatinine at 4 weeks after surgery remained stable at 1.05 mg/dL.

Which are the known risk factors for development of RCC?

a. Smoking
b. ESKD
c. Hypertension
d. Obesity
e. All of the above

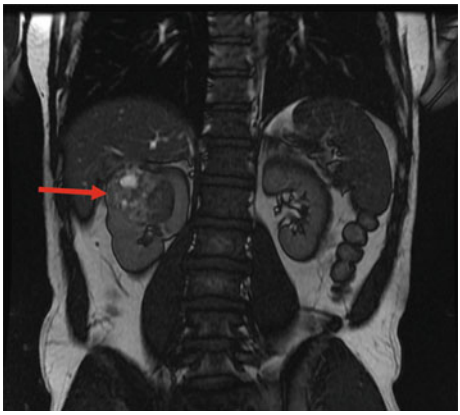

Fig. 9.1 Case presentation: MRI, coronal section, revealing heterogeneous right renal mass

Basic Epidemiology and Risk Factors of Kidney Cancer

Kidney cancer or RCC is the eighth most common cancer in men and the tenth leading cause of cancer-related death in men in the USA [1]. It accounts for 2–3 % of all adult malignancies. Of the estimated 1,660,290 new cancer cases in the USA in 2013, kidney and renal pelvis cancer combined will account for 40,430 (5 %) and 24,720 (3 %) new cancer cases in males and females, respectively. Similarly, of the anticipated 580,350 cancer deaths in 2013, kidney and renal pelvis cancer will account for 8780 (3 %) and 4900 (2 %) deaths in males and females, respectively [2].

Tobacco use has been shown to increase the risk of RCC up to twofold when compared with nonsmokers. This association demonstrates a dose–response relationship, with the number of packs per day or longer duration (pack-years) associated with an increased risk [3, 4] Compared with nonsmokers, smokers with RCC have poorer overall survival (6.6 years versus 4.2 years, respectively) [5]. Although increased body mass index has similarly been linked with a higher risk of developing RCC, [6, 7] obese individuals had better disease-free survival (DFS) when compared with those who were non-obese (5-year DFS of 80 % versus 72 %, respectively) [5, 8]. Obesity and hypertension have been shown to be modifiable risk factors among tobacco users [3]. The association of smoking with an increased risk of RCC was found in non-obese individuals (and not those with BMI $\geq 30\,Kg/m^2$) and in those who reported no prior history of hypertension.

Hypertension is associated with RCC in two distinct ways: as a risk factor predisposing to the development of RCC; and as a paraneoplastic syndrome associated with RCC. Patients with hypertension have up to a twofold increase in risk of developing RCC as compared to their age-matched controls [9, 10]. This risk is hypothesized to result from chronic inflammation or hypertension-induced renal injury, especially to the renal tubules, rather than from the use of antihypertensive medications [10, 11]. Hypertension may also develop in patients with RCC in the setting of a tumor involving the juxtaglomerular apparatus cells resulting in abnormally increased renin production. The activation of the renin–angiotensin–aldosterone pathway leads to

increased aldosterone and angiotensin synthesis with subsequent fluid retention and vasoconstriction. The downstream effect is an elevated blood pressure.

End-stage kidney disease (ESKD) has been identified as a risk factor for RCC, with up to a 100 % increase in incidence when compared with the general population. Although this increased risk was observed in both transplanted and dialysis-only patients, RCC was found to have more favorable clinical and pathological outcome features in individuals who have undergone renal transplantation [12, 13]. The difference in clinical outcomes in these settings, however, may be related in part to early detection bias. The patient with a transplanted kidney, followed by the urologist or the transplant surgeon or nephrologist, is more likely to have a tumor detected earlier than a dialysis-only patient, given the enhanced attention to the patients' native kidneys between the surgeon and the nephrologist. Hemodialysis for more than 10 years is associated with poorer outcomes and adverse histopathological features, e.g., acquired cystic disease-associated RCC and sarcomatoid differentiation. Hence, patients on long-term hemodialysis should have annual screening of their native kidneys after more than 10 years of dialysis [14, 15].

A high-fat or high-protein diet, occupational exposures to lead, aromatic hydrocarbons, rubber, asbestos, and radiation are also presumed to be associated with an increased risk of development of RCC but the available data are inconclusive [6, 11].

Case #1 Follow-Up and Discussion
As stated above, ESKD, smoking, and obesity have been linked with the development of RCC. In addition, hypertension can be seen as a risk factor and a paraneoplastic syndrome associated with RCC. Hence, the correct answer is e.

Histological Subtypes and Genetic Changes Associated with RCC

RCC occurs sporadically in the majority of patients, accounting for more than 95 % of the cases, with only about 2–3 % of the cases resulting from hereditary predisposition [11]. Genetic alterations or abnormalities predisposing to inherited forms of RCC have been described, with tumors often occurring in multiple sites in the same or in both kidneys at the same time (synchronous) or at different times (metachronous). The efforts of Linehan et al. at the US National Cancer Institute have led to the discovery and understanding of the close molecular link between histopathology, i.e., clear cell, papillary type 1, papillary type 2, chromophobe, and oncocytoma, and specific genetic abnormalities (Fig. 9.2).

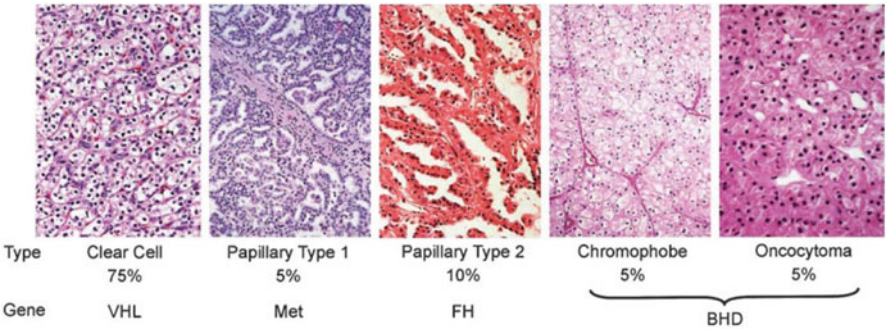

Fig. 9.2 Histologic types of renal cell carcinoma (*RCC*) and associated genetic alteration in hereditary RCC. (From Linehan et al. [16])

Clear Cell RCC

Clear cell RCC is the most common and well-studied histological variant of RCC, accounting for about 75 % of all the cases of RCC. Clear cell RCC may be sporadic or may occur in inherited forms in association with von Hippel–Lindau (VHL) syndrome, in which individuals are also at risk of developing tumors in the cerebellum, spine, retina, inner ear, pancreas, adrenal glands, and the epididymis [17]. In patients with VHL syndrome, tumors in the kidney may increase to 600 [18], hence nephron sparing surgery is generally preferred. Given that the risk of metastasis is very low in small tumors, surgical exploration and resection are recommended once the lesions have reached the size of ≥ 3 cm. Although it was discovered in the setting of hereditary clear cell RCC, the VHL gene is an early driver of sporadic RCC as well. The loss of VHL function by mutation or promoter DNA methylation can be identified in most cases of sporadic clear cell RCC [17, 19, 20].

The VHL gene is a tumor suppressor gene located on the short arm of chromosome 3 (3p). The downstream effect of either VHL mutation or methylation is the accumulation of hypoxia inducible factor (HIF) and the subsequent increased downstream transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-α (TGF-α) [21]. This ultimately leads to the increased angiogenesis and tumor cell proliferation. This mechanism or pathway is targeted by the newer systemic therapies for kidney cancer as discussed later in this chapter (Fig. 9.3).

Papillary Type 1 RCC

Papillary type 1 RCC accounts for approximately 5 % of all kidney cancers. The genetic abnormality associated with this histologic variant of RCC is activation of c-MET, an oncogene located on chromosome 7. Papillary renal tumors often demonstrate gains of chromosomes 3, 7, and 17, resulting in the increased activity

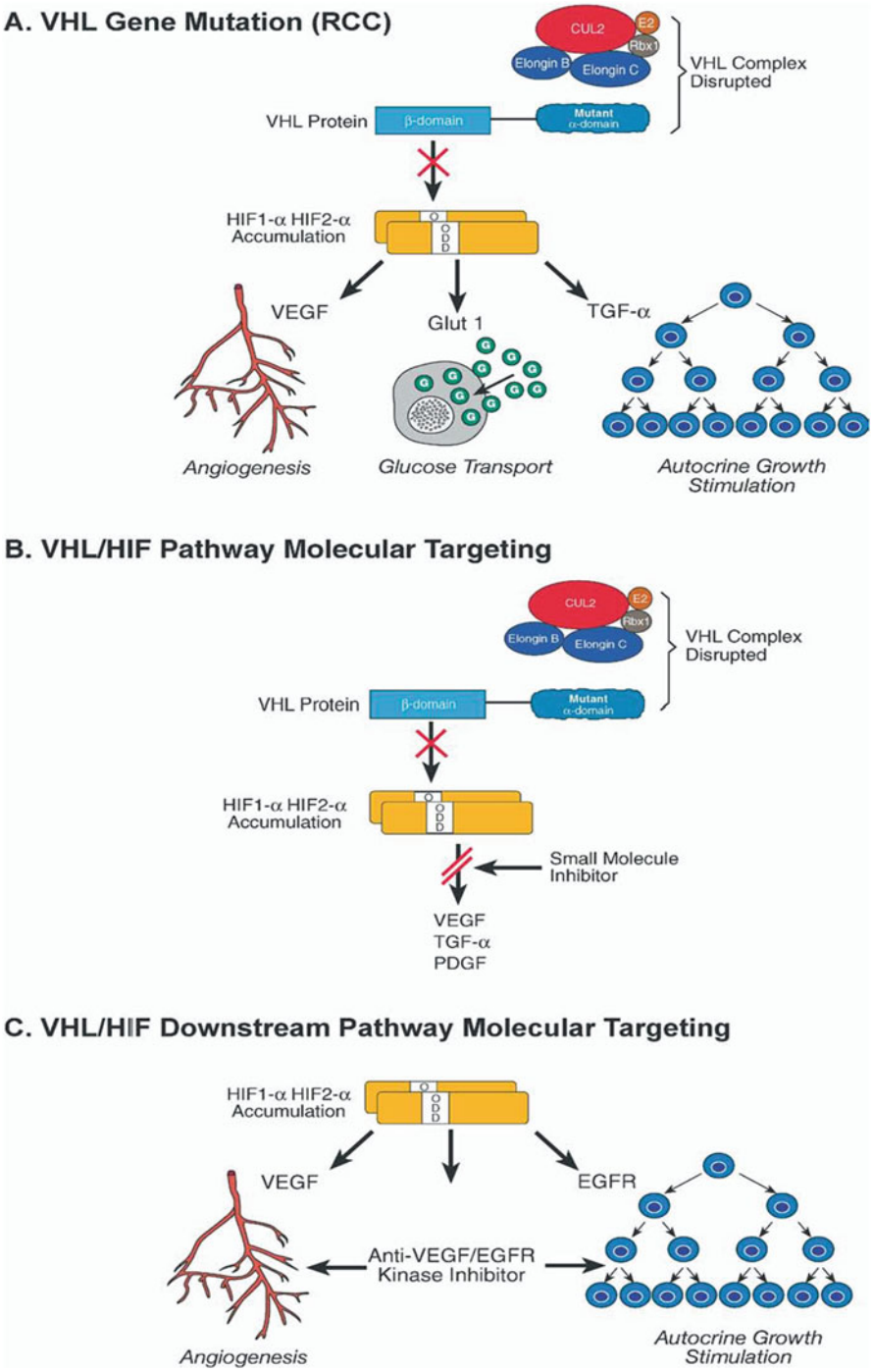

Fig. 9.3 The VHL gene complex—hypoxia-inducible factors (*HIF*) molecular pathway in pathogenesis of RCC and sites of therapeutic targets. (From Rosner et al. [22])

of c-MET. Individuals with hereditary papillary RCC (very rare) tend to develop multiple, and often bilateral, multifocal tumors. With the goal of renal preservation and excellent oncological outcome, these tumors are managed surgically by partial nephrectomy [21−24].

Papillary Type 2 RCC

Papillary type 2 RCC is an aggressive form of kidney cancer accounting for about 10 % of all RCCs. It can be found in both sporadic cases as well as in the context of hereditary leiomyomatosis RCC (HLRCC) syndrome. Along with kidney cancer, HLRCC is characterized by the associated findings of cutaneous leiomyomas and uterine fibroids. The syndrome results from an inactivating mutation in *fumarate hydratase*, a Krebs cycle enzyme. Given the aggressive nature of this variant of RCC, total/radical nephrectomy is generally recommended [21, 22, 25].

Chromophobe RCC and Oncocytoma

Chromophobe RCC and oncocytoma, each accounting about 5 % of RCC, are associated with Birt–Hogg–Dube (BHD) syndrome, either as a single entity or in combination (hybrid forms). In addition to developing renal tumors, which are often multifocal and bilateral, individuals with BHD syndrome are prone to developing fibrofolliculomas and pulmonary cysts. The genetic defect in BHD syndrome is a loss of function of the BHD gene on chromosome 17 (17p11.2), which functions as a tumor suppressor gene [21, 26]. Chromophobe RCC has been shown to have equivalent or even better cancer-specific survival outcomes when compared with clear cell or papillary RCC [27, 28].

Diagnosis and Staging

The majority of cases of RCC are now found incidentally during abdominal imaging for unrelated reasons. However, patients with renal tumors may present with flank/abdominal pain, hematuria, or symptoms of metastasis and/or a paraneoplastic syndrome. The gold standard diagnostic imaging technique is a computerized tomogram (CT) scan of the abdomen without and with intravenous (IV) contrast to determine enhancement characteristics of the mass. In patients who have an allergy to iodinated contrast or have renal insufficiency, magnetic resonance imaging (MRI) without and with gadolinium is recommended. In patients with chronic kidney disease (CKD) stage 4 (estimated glomerular filtration rate (eGFR) $\leq$ 30 mL/min), gadolinium contrast is contraindicated. If an MRI with contrast is absolutely necessary for a proper evaluation, a nephrology consultation should be sought, and two

sessions of dialysis separated by 2 days apart should be planned [29, 30]. Alternatively, in these patients, diffusion-weighted MRI (without gadolinium contrast) can be used to differentiate complex cystic and solid masses from benign lesions in the kidney [31].

Basic laboratory studies should be obtained including a complete blood count, comprehensive metabolic panel, urinalysis, and a chest radiograph. In individuals with an elevated corrected calcium level or alkaline phosphatase level, a nuclear medicine bone scan should be performed to evaluate for bone metastasis. With the presence of neurological symptoms or headaches, a CT or preferably an MRI of the brain should be obtained to evaluate the presence of central nervous system metastases. Other laboratory evaluations or imaging studies may be obtained as clinically indicated [32].

The TNM classification of RCC according to the AJCC 2010 staging is shown in Table 9.1.

Surgical excision of tumor or removal of the entire kidney, depending on the size and other criteria is a diagnostic approach of choice for kidney cancer. In certain clinical scenarios, such as a high-risk surgical candidate, the existence of a solitary kidney, the suspicion of secondary metastasis to the kidney, or patients considered for active surveillance or observation of their kidney tumor (in the case of small tumors), image-guided biopsy of the kidney tumor should be considered. With current CT, MRI, and biopsy techniques available, renal biopsy can accurately predict the histology of renal masses, thus helping to stratify patients into risk categories and determine those that may qualify for active surveillance. Halverson et al. [33] evaluated the utility of a kidney biopsy in stratifying patients into various risk groups by analyzing 151 patients with small renal masses who underwent kidney biopsy prior to extirpative surgery. They reported an agreement between kidney biopsy and final pathology in 97 % of the cases, with a negative predictive value of 0.86 and a positive predictive value of 1.0 [33]. Furthermore, a review of the published evidence regarding the use of kidney biopsies reported in the American Urological Association (AUA) guidelines revealed a sensitivity and specificity of up to 99.5 and 99.9 % respectively [34].

Active Surveillance (AS) for Renal Masses

Although the preferred choice of treatment for operable renal tumors is surgical extirpation, a clinical decision may be made to actively observe a renal mass (usually in the case of small renal masses), especially in the elderly patient with multiple comorbidities rendering them as high-risk for general anesthesia. Mason et al. [35] actively followed 84 patients with renal masses ranging from 0.8 to 5.4 cm at diagnosis for a median duration of 36 months (range: 6–96 months). They reported that only one patient (1.2 %) developed metastases during follow-up. The mean growth rate of renal masses was reported to be 0.25 cm/year, with tumors $\geq$ 2.45 cm in its largest diameter at the time of diagnosis exhibiting a faster growth rate during follow-up [35].

Table 9.1 AJCC 2010 staging of primary kidney tumor, lymph node involvement, and distant metastasis. (Source: Adapted from Edge SB, Byrd DR, Compton CC, et al. eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp. 479–89)

	Description	
T stage	Tx	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney
	T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidney
	T1b	Tumor > 4 cm but not > 7 cm in greatest dimension, limited to the kidney
	T2	Tumor > 7 cm in greatest dimension, limited to the kidney
	T2a	Tumor > 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney
	T2b	Tumor > 10 cm, limited to the kidney
	T3	Tumor extends into major veins or perinephric tissues but not beyond Gerota's fascia
	T3a	Tumor grossly extends into the renal vein or its segmental branches, or tumor invades peri-renal or renal sinus fat but not beyond Gerota's fascia
	T3b	Tumor grossly extends into the IVC below the diaphragm
	T3c	Tumor grossly extends into the IVC above the diaphragm or invades the wall of the IVC
	T4	Tumor invades beyond Gerota's fascia (including *contiguous* extension into the ipsilateral adrenal gland)
N stage	Nx	Regional lymph nodes cannot be assessed
	N0	No evidence of regional lymph node metastasis
	N1	Metastases in regional lymph node(s)
M stage	M0	No evidence of distant metastasis
	M1	Distant metastasis present

Hence, in a carefully selected group of patients, AS may be a valuable option and kidney biopsy may be an adjunct in the management, as mentioned above [33, 34].

Surgical Management of Renal Masses

The mainstay of treatment of clinically localized RCC is excision based on the recommendations of the National Comprehensive Cancer Network (NCCN) [32], with the option of radical or nephron-sparing surgery (NSS), the latter commonly referred to as partial nephrectomy.

Radical Nephrectomy

The NCCN guidelines recommend radical nephrectomy (RN; surgical removal of the entire kidney and Gerota's fascia +/− removal of the ipsilateral adrenal gland) in patients with kidney tumor measuring > 10 cm in its largest diameter or in patients with multiple kidney tumors in the same kidney but without genetic predispositions as described above. This treatment option is based on evidence that suggests a high risk of recurrence following surgery. However, as described below, the evidence is inconclusive as to the superiority of radical nephrectomy over partial nephrectomy in terms of renal functional or oncological outcomes [36−38].

Partial Nephrectomy

Partial nephrectomy (PN) (also termed nephron sparing surgery (NSS)) is the gold-standard for the treatment of patients with small renal masses (SRMs)(≤ 4 cm or T1a), although it is increasingly utilized for T1b tumors (4–7 cm, confined to the kidneys) [32]. This can be done via a traditional open incision, a laparoscopic approach with or without the assistance of a robotic system, and has been shown to be safely performed, even in old patients [39]. Variations in technique that include clamping the hilar vessels during tumor extirpation (goal clamp time ≤ 30 min), selective clamping of renal vessels (*zero ischemia)* [40, 41], and without clamping of hilar vessels (*off-clamp)* [42] even for complex or hilar [43] renal tumors have been described. Reducing or eliminating warm ischemia (time in which a tissue or an organ remains at body temperature after its blood supply has been cut off before it is perfused or cooled) is thought to reduce damage to nephrons from ischemia and the release of damage-inducing free radicals.

The goal of a partial nephrectomy is to spare residual normal nephrons, thus preserving renal function, particularly in patients who at the time of diagnosis have some form of CKD. However, studies evaluating renal functional outcomes following partial nephrectomy have reported conflicting results. van Poppel et al. [37], in a randomized trial comparing partial versus radical nephrectomy for low-stage renal tumors, reported a 10-year overall survival rates of 81.1 % for radical nephrectomy and 75.7 % for nephron-sparing surgery (*superiority p-value = 0.03)*. On the other hand, Tan et al. [38], in a retrospective analysis of Medicare beneficiaries with T1a tumors, reported a significantly improved overall survival with partial nephrectomy when compared with radical nephrectomy, albeit with the caveat of unknown confounders regarding other risk factors.

With respect to renal functional outcomes, the European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized trial by comparing nephron-sparing surgery versus radical nephrectomy. After a median follow-up of 6.7 years, Scosyrev et al. [44] reported a significant reduction in the incidence of moderate renal dysfunction (eGFR < 60 mL/min; 64.7 % for NSS versus 85.7 % for RN, respectively). Although not statistically significant, NSS was associated with a reduced incidence of advanced kidney disease (eGFR < 30 mL/min; 6.3 % and

10.0 %, respectively). However, the incidence of kidney failure (eGFR < 15 mL/min) was essentially identical between NSS and RN (1.6 % versus 1.5 %, respectively), and the impact of NSS on renal functional outcomes did not translate into an improved overall survival in this trial [44].

On the other hand, a study of a community-based population evaluating the impact of medical renal disease, demonstrated the risk of death to increase as GFR decreases below 60 mL/min, with hazard ratios ranging from 1.2 (with an eGFR of 45–59 mL/min) to 5.9 (with an eGFR of < 15 mL/min per 1.7 m^2 of body-surface area). An inverse relationship was also observed between eGFR and the risk of cardiovascular events and hospitalization [45]. While NSS has not been shown to improve the overall survival outcome, this study indicates the importance of prevention of chronic renal insufficiency and the need to perform nephron-sparing surgery for renal masses when possible without compromising on oncologic outcomes.

Percutaneous Ablation

Although extirpative surgery is the mainstay of treatment of kidney tumors, percutaneous ablation is a safe and effective option and can be successfully employed in patients with multiple comorbidities who are not surgical candidates. Two modalities that have been popularized are cryoablation and radiofrequency ablation (RFA). Cryoablation involves the delivery of freezing temperatures (up to—50 °C) via probes (in a freeze-thaw cycles) to cause tissue destruction by an immediate direct cellular damaging effect and by a delayed vascular mechanism, with hypoxia-ischemia resulting from microvascular stasis during cooling [46, 47]. Alternatively, RFA involves the use of high-frequency alternating current, causing frictional heating from electrons flowing near the site of energy delivery. At temperatures 49 °C and above, cell death results from enzyme inactivation, denaturation of proteins, and irreparable damage to cellular membranes [48, 49].

In a meta-analysis comparing cryoablation and RFA, El Dib et al. [50] reported a clinical efficacy of 89 % and 90 %, respectively, for these two modalities in the management of patients with small renal masses (≤ 4 cm). This analysis showed no statistically significant difference in complication rates between cryoablation and RFA. While these ablation techniques may be a reasonable approach, they are limited by the paucity of long-term follow-up data and difficulty in evaluating patients for either recurrence or the presence of residual tumor following treatment [50].

Cytoreductive Nephrectomy

Unlike some other solid organ tumors, surgical removal of the kidney in the setting of metastatic kidney cancer (cytoreductive nephrectomy) has been shown to be associated with an improved overall survival. Motzer et al. [51] identified the absence of a prior nephrectomy as one of the five prognostic factors predicting shorter overall survival in patients with advanced RCC. Cytoreductive nephrectomy was

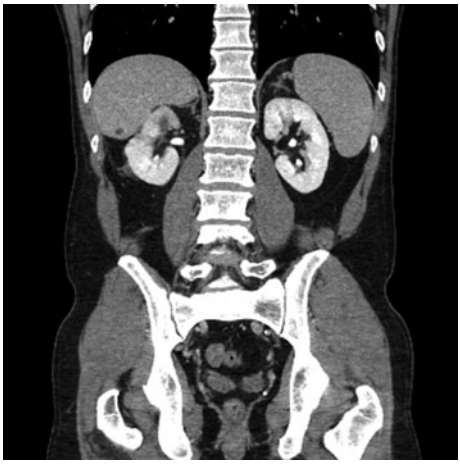

Fig. 9.4 Case presentation: Postoperative CT scan 6 months after surgery revealing well-perfused right kidney with cortical defect at the site of prior resection

evaluated in two prospective randomized controlled trials, both demonstrating an increase in overall survival favoring surgical intervention along with interferon versus interferon alone [52, 53]. The combined analysis of these two trials demonstrated a median survival of 13.6 months for the cytoreductive nephrectomy plus interferon cohort as compared with 7.8 months for interferon alone, corresponding to a 31 % decrease in the risk of death ($p = 0.002$) [54].

Several mechanisms have been proposed to explain the observed survival improvement following cytoreductive nephrectomy. Although all theoretical, the proposed mechanisms include reduced tumor burden, reversal of the associated immunosuppressive milieu within the primary tumor, and reduction in the amount of circulating angiogenic factors, such as VEGF [55].

Case #2

AA had surgery. Six months following surgery, he underwent surveillance imaging including CT scan of the chest, abdomen, and pelvis (Fig. 9.4). The imaging revealed no evidence of local recurrence within the kidney, but did reveal several enhancing retroperitoneal lymph nodes in the paracaval and interaortocaval regions. The lymph nodes were worrisome for metastatic recurrence. At the current time, he is weighing his options of surgical resection versus immunotherapy with high-dose interleukin 2 versus molecular-targeted therapy with sunitinib maleate.

What major side effect of Interleukin 2 leads to significant hypotension and acute kidney injury?

a. Thrombotic microangiopathy
b. Capillary Leak Syndrome
c. Minimal Change Disease
d. None of the above
e. All of the above

Medical Treatment of Metastatic Renal Carcinoma

The natural history of RCC is quite variable and may be marked by prolonged stability of metastatic disease in some instances. Late relapses after nephrectomy, some decades later, may occur. In addition, there are reports of spontaneous regression of metastases after cytoreductive nephrectomy [56]. Treatments from the remote past have included hormonal agents and multiple small trials of various chemotherapy drugs. Medroxyprogesterone (MPA) was first utilized many years ago; it was associated with a small percentage of responses and, given the lack of response with cytotoxic chemotherapy, was prescribed in the metastatic setting. Since then, as described below, there have been several advances in immunotherapeutic and molecular-targeted therapeutic agents in metastatic kidney cancer.

Prognostic Stratification

Prognostic factors have become important stratification variables in clinical trials of agents for the treatment of metastatic RCC. The behavior of metastatic RCC is quite variable and some patients with low-disease burden and favorable prognostic features after nephrectomy may be followed for evidence of progression prior to the initiation of treatment [57]. There are a few patients that may not require treatment at all in the setting of asymptomatic indolent disease in the face of competing comorbidities. Others may have rapid progression of disease. With this disease heterogeneity in mind, a review of patients treated on prior chemotherapy and immunotherapy clinical trials at Memorial Sloan-Kettering Cancer Center (MSKCC) identified five prognostic factors that could be used to stratify patients into one of three prognostic groups. The five factors identified are: a Karnofsky performance status (KPS) of less than 80 %, low hemoglobin value (less than lower limit of normal), high corrected calcium level ($>$ 10 mg/dL), high LDH level ($>$ 1.5 times the upper limit of normal), and less than 1 year from the time of nephrectomy to metastases. The presence of three or more risk factors results in the shortest overall survival and comprises the poor-risk group. Patients with one or two factors are considered intermediate-risk and the absence of any of these factors, the favorable-risk group. In the initial study, the 3-year survival rate among patients treated with cytokines was 31, 7, and 0 % for the favorable-risk, intermediate-risk, and poor-risk groups, respectively [51].

Given that the MSKCC schema was developed in the cytokine era, additional risk-stratification systems have been proposed more recently. Prior radiotherapy and the number of metastatic sites were added to the MSKCC scoring system in a model from the Cleveland Clinic [58]. Heng et al. proposed a new model for patients treated in the current era of targeted therapy from a cohort of consecutive patients that were treatment naive and had received sunitinib, sorafenib, or bevacizumab on clinical trial. Using overall survival as the endpoint, 16 potential predictive covariates were assessed in univariate and multivariate analyses. In the final analysis, four of the five predictive factors from the original MSKCC criteria remained significant.

Additionally, an elevated absolute neutrophil count and an elevated platelet count (both above the upper limit of normal) were predictive of worse outcome. The authors reported 2-year overall survival probability of 75, 53, and 7 % for the favorable-risk, intermediate-risk, and poor-risk groups, respectively [59].

Progression-free survival (PFS) is the most utilized trial endpoint as the use of multiple agents in succession as well as crossover in many trials have made the assessment of overall survival (OS) problematic [60]. A large retrospective analysis from consecutive patients treated with targeted agents at 12 cancer centers in North America revealed that lack of disease progression at 3 and 6 months intervals independently predicted improved overall survival. The conclusion from the authors was that there is a dependent relationship between PFS and OS in metastatic RCC patients treated with current targeted agents [61]. This has led to the use of the endpoint of PFS as an acceptable determinant of benefit in clinical trials in RCC.

Immunotherapy

Interferon-Alpha

Interferon-alpha was shown to improve overall survival of patients in a randomized controlled trial against medroxyprogesterone acetate, an agent that had been utilized for metastatic RCC based on occasional tumor responses. The primary endpoint of the trial was OS and the interferon group had a superior outcome, with a 2.5-month improvement in survival (median OS 8.5 months versus 6 months for MPA) [62]. Interferon-alpha did not receive regulatory approval for the treatment of metastatic RCC in the USA but became the standard of care for many years. This was evident in the two trials conducted in the USA and Europe that established cytoreductive nephrectomy as the standard of care. Patients deemed eligible for a cytoreductive nephrectomy were randomized to surgery with interferon treatment versus interferon alone. Patients who underwent cytoreductive nephrectomy were found to have a 5.8-month median survival advantage [54]. However, the trial also established that the response to interferon was modest, underscored by a recently published negative trial by the French Immunotherapy Group. In 2005, a Cochrane review by Coppin et al. concluded that interferon-alpha provided modest survival benefit and (in the pre-targeted therapy era) cytoreductive nephrectomy followed by interferon-alpha provided the best outcomes in surgically fit patients [63].

Interleukin-2

Interleukin-2 received regulatory approval in 1992 based on uncontrolled experience demonstrating objective responses, including several complete responses. More importantly, a proportion of those complete responders proved to be durable in long-term follow-up. In a retrospective review of the experience at the US National

Institutes of Health ($n = 259$ patients), perhaps the largest national experience, the overall objective response rate was 20 %, with 23 patients experiencing a complete response (CR) and 30 patients achieving a partial response (PR). Only four of those complete responders remained without evidence of disease at the time of last assessment [64].

Given the potential toxicity, high-dose IL-2 (preferred over low dose IL-2) is administered in limited centers in the USA. The usual dose planned is 720,000 IU/kg administered IV over 15 min every 8 h for a total of 15 doses. Since many patients do not tolerate the total number of doses, the investigators at the NCI proposed to reduce the number of doses to 12 per cycle. Two cycles constitute one course of treatment, with usual plan of administering two courses. Profound hypotension and oliguria are common significant adverse events resulting from capillary leak syndrome and often require an intensive care unit admission during treatment. Additionally, patients can experience confusion and a depressed level of consciousness. Given the high incidence of grades 3–4 toxicity, patient selection is very important in this potentially curative treatment where durable remissions have been noted to occur [62]. The ideal patient is generally younger with an excellent performance status, pulmonary only metastasis, previous nephrectomy, and no significant cardiovascular comorbidities. Given the potential for complete and durable response, high-dose IL2 has become the standard of care immunotherapy for metastatic kidney cancer in well-selected patients.

Tyrosine Kinase Inhibitors (TKIs)

The addiction of clear cell carcinoma to the VEGF pathway led to the development of several agents targeting this pathway for use in metastatic RCC. Four agents are currently approved for use in the USA, and each targets the VEGF receptor. Sorafenib and sunitinib were approved in 2006. Subsequently, pazopanib and axitinib achieved regulatory approval based on benefits demonstrated in randomized Phase 3 trials.

Sorafenib was compared to placebo in patients who previously received cytokine therapy (defined as IL-2 or interferon-alpha), demonstrating a PFS benefit in comparison to placebo of 5.5 months versus 2.8 months, respectively ($p < 0.00001$, hazard ratio 0.44). Sorafenib blocks the kinase domain of the VEGF receptor (VEGFR)-2, VEGFR-3, platelet derived growth factor receptor (PDGFR)-β, as well as RAF-1, Flt-3, and c-KIT. The original primary end-point of the trial was OS, yet 48 % of the patients on placebo crossed over to receive sorafenib [65]. A post-hoc analysis of the trial, with censoring of those patients that crossed over from placebo to sorafenib, suggested an OS benefit. In the intention-to-treat analysis, OS was 17.8 versus 15.2 months for sorafenib versus placebo, respectively. After censoring the crossover patients, OS was 17.8 versus 14.3 months, (HR 0.78, $p = 0.029$). This result is suggestive of an improved overall survival, with caveat that higher proportion of good-risk patients crossed over to receive sorafenib. Sorafenib did not have a PFS benefit over interferon-alpha in the first-line treatment of metastatic RCC in

a randomized Phase 2 trial [66]. Sorafenib has modest efficacy in the second-line treatment of metastatic RCC after sunitinib or bevacizumab, with an objective response rate of less than 10 % and a median PFS of 4.4 months [66]. Sorafenib has been used as the control arm for trials in the development of subsequent agents.

Sunitinib maleate inhibits multiple receptor tyrosine kinases including PDGFR-α and -β, VEGFR-1, -2 and -3, c-KIT, Fms-like tyrosine kinase-3 (FLT-3), CSF receptor-1 and neurotrophic factor receptor (RET) [67]. The sunitinib registration trial compared this agent in treatment-naive patients to interferon-alpha, revealing a PFS benefit of 11 months versus 5 months, favoring sunitinib. OS improvement was not reported as the median survival had not been reached in the pre-planned early analysis for PFS [68]. There was limited crossover to sunitinib on this trial (7 % of interferon-treated patients received sunitinib). In the intention-to-treat analysis, OS was 26.4 months versus 21.8 months, respectively, for sunitinib compared with the interferon-treated group ($p = 0.51$). In an exploratory analysis of OS with censoring of those who crossed over, the median OS was 26.4 versus 20 months, respectively, for sunitinib versus interferon ($p = 0.036$) [69].

Pazopanib targets VEGF-R-1, -2 and -3, PDGFR-α and -β, fibroblast growth factor receptor (FGF-R)-1 and -3 and c-Kit. It was approved in the USA in 2010 based on a randomized controlled trial versus placebo in treatment-naive individuals and cytokine pretreated individuals, revealing a PFS of 9.2 months for the pazopanib arm versus 4.2 months for the placebo-treated individuals. This trial was conducted in countries where other agents were generally not available and thus placebo was utilized as the control arm [70]. The PFS for the treatment-naive population was 11.1 months for pazopanib versus 2.8 months for placebo. Pazopanib-treated patients were noted to have total objective response rate of 30 %, and disease stability in an additional 38 % [70].

In a comparison trial of pazopanib and sunitinib designed as a non-inferiority comparison for treatment-naive patients, median PFS was similar in both arms, at 10.5 months for pazopanib and 10.2 months for sunitinib. The results met the pre-trial assessment for non-inferiority. Health-related quality of life parameters were assessed with significant differences favoring pazopanib in 11 of 14 comparisons [71]. Pazopanib and sunitinib are both considered first-line receptor TKI-targeted treatments for treatment-naive patients.

Axitinib is the most recent TKI to receive approval in the USA for the treatment of metastatic RCC. It is a potent and selective second-generation inhibitor of VEGFR-1, -2, and -3 with a relative potency of 50–450-fold greater than first generation VEGFR inhibitors. This agent was compared to sorafenib in second-line treatment after the failure of one TKI. The trial demonstrated improved PFS: 6.7 months for axitinib treated patients versus 4.7 months for sorafenib treated patients (OS, 11.9 versus 9.1 months, respectively) [72]. Axitinib is currently approved as second line or later treatment in patients who have previously received a TKI.

mTOR Inhibitors

Mammalian target of rapamycin (mTOR) signaling is prominent in many tumor types including kidney cancer, and two agents are currently approved in the USA as treatment for metastatic RCC. Temsirolimus is an intravenously administered mTOR inhibitor, given on a weekly basis, and approved for poor-risk metastatic RCC patients. This agent was evaluated among poor-risk metastatic RCC in a three-arm trial including temsirolimus monotherapy, interferon-alpha monotherapy, and combination temsirolimus/interferon alpha. Patients enrolled in this trial had to have three or more MSKCC risk criteria, thus comprising a poor-risk group. In addition to the MSKCC criteria, metastasis in multiple organ sites was included as a sixth risk factor. The temsirolimus arm demonstrated an improved overall survival as well as an improved PFS. Of note, temsirolimus is the only targeted therapy with statistically significant OS benefit in a randomized control trial. The PFS for temsirolimus was 5.5 months versus 3.1 months for the interferon group. The OS was 10.9 months for temsirolimus compared to 7.3 months for the interferon alone arm. The combination arm had similar outcomes to the interferon alone arm, albeit with greater toxicity [73]. This trial also permitted the enrollment of patients with non-clear cell histology comprising approximately 20 % of the study population.

Everolimus is an orally available mTOR inhibitor, which was studied in patients that were previously treated with either sunitinib or sorafenib. At the time of the trial, there was no approved second line agent. Therefore, in this trial, the comparator group was administered placebo. The results showed PFS of 4.9 months for everolimus versus 1.9 months for placebo. These findings led to regulatory approval of everolimus as second-line treatment after failure of one TKI treatment [74].

Bevacizumab and Interferon Combination

The AVOREN trial compared bevacizumab plus interferon-alpha versus interferon alone. Bevacizumab is a monoclonal antibody directed against VEGF. The trial demonstrated PFS of 8.2 months versus 5.2 months favoring the treatment arm. All patients had either cytoreductive or previous nephrectomy and the majority of subjects consisted of intermediate-risk individuals. Objective response rates were also higher in the bevacizumab treated patients, 31 % versus 13 % in the interferon only arm. In a similar trial design, Rini et al. also demonstrated a superior PFS with the addition of bevacizumab, at 8.5 months for the combination arm and 5.7 months for the interferon alone arm. Similar to the AVOREN trial, prior nephrectomy occurred in 85 % of the trial population [75]. In the final analysis of this trial, OS favored the bevacizumab arm, but did not meet the predefined criteria for significance. The hazard ratio was 0.86 (95 % confidence interval: 0.73–1.01) [76]. Overall response rates were 25.5 % for the combination arm versus 13 % for the interferon alone arm.

Bevacizumab Monotherapy

As a result of the toxicity associated with interferon-alpha treatment of RCC, many physicians utilize monotherapy with bevacizumab. A randomized trial of bevacizumab (at 2 dose levels) versus placebo in cytokine pretreated patients was conducted and published in 2003. PFS was superior to placebo at the second interim analysis in the higher dose level and the trial was halted for further accrual. The PFS was 4.8 months versus 2.5 months for bevacizumab versus interferon, respectively. The objective response rate was 10 %. Overall survival was not significantly improved [77].

Non-Clear Cell RCC

Management of patients with non-clear cell histology is beyond the scope of this chapter. Collecting duct carcinomas have been shown to possibly benefit from cisplatin-based combination chemotherapy with some responses noted in a prospective Phase 2 trial (objective responses rate 26 %) [78]. Sarcomatoid histology is often seen in high-grade clear cell RCC and is considered an aggressive variant. In a small trial of 18 patients with predominant sarcomatoid histology, two complete responses and four partial responses were noted in patients treated with a combination of gemcitabine and doxorubicin [79]. The relatively small number of cases and the limited clinical trial opportunities have resulted in a void as to the optimal management of these patients in the era of targeted therapy.

In an analysis of the expanded access cohort for sunitinib, the non-clear cell histology group revealed an overall response rate of 11 %. PFS was 7.8 months with an OS of 13.4 months, significantly less than the clear cell patients treated on the Phase 3 trial. The total cohort consisted of greater than 4000 patients with all histologic types, with a PFS of 10.9 months and an OS of 18.4 months [80].

Toxicity Management of Targeted Agents

The targeted agents discussed above and outlined in Table 9.2 require skilled professionals in the management of the significant toxicity associated with these agents. These “off-target” adverse events are capable of producing significant issues in terms

Table 9.2 Currently approved medical therapies for clear cell RCC

Agent	Indication	Mechanism of action	Dosage and administration	Side effects
Interleukin-2	First-line therapy	Potentiation of T-cell activity	600, 000 IU/kg/dose IV every 8 h for 5 days (ICU setting)	Nausea, vomiting, diarrhea, fatigue, flu-like symptoms; vascular-leak syndrome (hypotension, third-spacing edema)
Sunitinib	First-line therapy Second-line therapy after failed cytokine or another TKI	Inhibition of tyrosine kinases: VEGFR-1, 2,3; PDGFR-α, β; c-KIT; FLT-3; CSF-1R; RET Inhibition of angiogenesis and cell proliferation	50 mg PO daily x 4 weeks, then 2 weeks off (6-week cycle)	Diarrhea, fatigue, hand–foot syndrome, hypertension, neutropenia, thrombocytopenia, systolic dysfunction, hypothyroidism, adrenal insufficiency
Pazopanib	First-line therapy Second-line therapy	Inhibition of tyrosine kinase: VEGFR-1, 2,3; and PDGFR-α, β	800 mg PO daily	Diarrhea, nausea, vomiting, anorexia, fatigue, weakness, hypertension, hair color changes, abdominal pain, hepatotoxicity, arrhythmias
Axitinib	Second-line therapy	Selective tyrosine kinase inhibition: VEGFR-1, 2, 3	Initial dose of 5 mg PO twice daily. Minor toxicity: 7–10 mg PO twice daily; Significant toxicity: 2–3 mg PO twice daily	Hypertension, fatigue, diarrhea, nausea, dysphonia, hypothyroidism
Sorafenib	Second-line therapy	Inhibition of tyrosine kinases: VEGFR-1, 2,3; PDGFR-α, β; c-KIT; FLT-3; CSF-1R; RET	400 mg PO twice daily (until clinical progression)	Hypertension, diarrhea, fatigue, rash, hand–foot syndrome, alopecia

Table 9.2 (continued)

Agent	Indication	Mechanism of action	Dosage and administration	Side effects
Bevacizumab	First-line therapy Second-line therapy after failure of cytokine or TKI	Neutralizes circulating VEGF-A	18–30 million IU/day, 3x/per week subcutaneously *Or* 10 mg/kg IV every 2 weeks	Hypertension, bleeding
Temsirolimus	First-line therapy (poor-risk category, 3–6 modified Motzer criteria) Second-line therapy after failure of cytokine or TKI	Inhibition of mTOR	25 mg IV weekly (until disease progression)	Mucositis, rash, hyperglycemia, hyperlipidemia, pulmonary complications
Everolimus	Second-line therapy	Inhibition of mTOR	10 mg PO daily	Stomatitis, rash, fatigue, infections

RCC renal cell carcinoma, *ICU* intensive care unit, *TKI* Tyrosine kinase inhibitor, *VEGFR* Vascular endothelial growth factor receptor, *PDGFR* Platelet-derived endothelial growth factor receptor, *c-KIT* stem cell factor receptor, *FLT-3* FMS-like tyrosine kinase, *CSF-1R* colony stimulating factor, *RET* neurotrophic factor receptor, *mTOR* mammalian target of rapamycin

of quality of life for individual patients, and patient education is critical in order to maintain safe administration and dose intensity.

Uncontrolled hypertension, decreased cardiac function, hypothyroidism, hand–foot syndrome, and many other adverse events require vigilance and prompt management interventions. Renal abnormalities may also be caused by many of the agents, including proteinuria (occasionally in the nephrotic range), thrombotic microangiopathy, and interstitial nephritis among other described entities. The inability to perform a kidney biopsy limits the interpretation of causation in these individuals as most patients usually have a solitary kidney after excision of their malignancy [81]. Treatment with TKIs for 6 months or greater in an expanded access program revealed a higher cumulative incidence of National Cancer Institute-Common Terminology Criteria for Adverse Events grade 3 or 4 events compared to patients treated less than 6 months, underscoring the vigilance required on the part of the prescriber. An overview of toxicity and management recommendations can be accessed in the citation by Eisen et al. [82]. In addition, an entire chapter is dedicated in this book on renal toxicities of biological agents as the ones used in RCC treatment.

Case #2 Follow-Up and Discussion
Based on above discussion, capillary leak syndrome (b) is the correct answer. Thrombotic microangiopathy is usually seen in TKIs and anti-VEGF agents. Minimal-change disease has been reported in TKIs.

Summary

Active surveillance may be considered in the management of small renal masses, especially in individuals who are not surgical candidates. Surgical treatment for renal masses includes partial or radical nephrectomy via an open approach or laparoscopy with or without the use of robot assistance. Although image-guided percutaneous ablative therapies are utilized, data regarding long-term oncologic and renal functional outcomes are not yet available. The era of targeted therapy for RCC has seen the development of several agents that have improved upon the prior treatment paradigm of the cytokine era. Sequencing of the use of these medications is becoming clearer with experience and new data. Combinations of therapy have generally resulted in increased toxicity without concomitant improvements in efficacy. Management of the treatment-related adverse effects requires in depth understanding of the "off target" effects in order to maintain patients on therapy with the best possible outcomes for survival and for quality of life.

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Chapter 10
Renal Cell Carcinoma and Chronic Kidney Disease

Mitchell H. Rosner

List of Abbreviations

CKD	Chronic kidney disease
EORTC	European Organization for Research and Treatment of Cancer
ESKD	End stage kidney disease
GFR	Glomerular filtration rate
RCC	Renal cell cancer

Case #1

A 65-year-old man with a 22-year history of type 2 diabetes mellitus, hypertension, hyperlipidemia, and stage 3a chronic kidney disease (CKD) (estimated glomerular filtration (eGFR) of 53 ml/min/1.73 m^2) has been diagnosed with a 6.4 cm solid renal mass in the lower pole of his left kidney. The mass appears to be contained within the renal capsule and no lymphadenopathy or signs of metastatic disease are seen. The patient undergoes a radical nephrectomy and the pathology is read as localized papillary renal cell carcinoma (RCC) without extension beyond the renal capsule. Incidental note is made of the finding of severe nodular glomerulosclerosis and moderate interstitial fibrosis consistent with diabetic nephropathy. The patient has never seen a nephrologist and he was unaware that he had CKD. Postoperatively, the patient had a stable course and 2 months later repeat laboratory work reveals an eGFR of 41 ml/min/1.73 m^2. He is now referred to a local nephrologist.

What is the most common parenchymal findings noted by the pathologists on renal tumor nephrectomies?

a. Diabetic nephropathy

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b. Focal segmental glomerulosclerosis
c. Hypertensive nephrosclerosis

According to the US National Cancer Institute, more than 65,000 cancers of the kidney and renal pelvis will be diagnosed in 2013 [1, 2]. While survival is generally good in this population it is estimated that there will be 13,680 deaths directly attributable to renal cell carcinomas (RCC) [1, 2]. Over the past two decades, there has been a notable migration toward the diagnosis of early stage kidney cancers in the USA. According to one study, 43 % of kidney cancers were stage I in 1993, but now comprise over 60 % of tumors [3, 4]. Earlier diagnosis is likely due to a myriad of findings including more aggressive imaging of patients with microscopic hematuria as well as an increased number of incidental diagnosis (an imaging study was done for an unrelated purpose and the renal mass was diagnosed). While, approximately 20–25 % of these small renal masses are benign (oncocytoma or angiomyolipoma), the majority are malignant and include the subtypes of clear cell carcinoma (70–7 % of malignant tumors), papillary (10–15 %), chromophobe (5–10 %), and oncocytic (3–7 %) [5, 6]. Depending upon the specific subtype and stage, the 5-year survival exceeds 90–95 % in most studies [7]. Importantly, there are currently more than 300,000 kidney cancer survivors in the USA. Given the excellent oncologic outcomes for a majority of patients with RCC, it is critical that care of these patients move beyond therapy that addresses the malignancy to those issues that affect long-term mortality and morbidity. In this population, CKD, due to both underlying conditions as well as loss of renal mass, has become a key determinant of long-term outcomes.

Surgical Management of the Patient with RCC

Given that over 60 % of patients with RCC are diagnosed with small renal masses (here defined as < 4 cm), there has been an evolution in the management of these patients as defined by two recent consensus statements from the American Urological Association and the European Association of Urology [8, 9]. Driving these changes is the fact that while advanced RCC is often lethal, surgically treated localized tumors < 4 cm (T1a) carry an excellent prognosis with a > 90 % 10-year recurrence-free survival rate [7, 10]. Thus, the era of radical nephrectomy (defined as complete resection of the kidney, adrenal gland, and local lymphadenectomy) as a "one-size fits all" strategy has been replaced by a more conservative strategy that includes a biopsy to confirm the diagnosis followed by nephron sparing treatment (partial nephrectomy) with localized tumor resection [8, 9]. For many other patients with small renal masses surveillance with sequential imaging over time may be an option as well.

Partial nephrectomy had been a treatment option that was mostly utilized for specific patient populations where end-stage kidney disease (ESKD) might result if more radical surgery was utilized (such as disease in a solitary kidney, bilateral renal tumors or in the setting of severe CKD). The evidence supporting partial nephrectomy for

small renal masses emerged in the 1990s with studies demonstrating equivalent 10-year oncologic outcomes between partial nephrectomy and more radical approaches [11–13]. However, the controversial European Organization for Research and Treatment of Cancer (EORTC) trial cast some debate on whether partial nephrectomy had similar mortality results to radical nephrectomy [14]. This is the only trial where 541 patients with solitary renal masses < 5 cm were randomized to either partial or radical nephrectomy over a 5-year accrual period. The results from the EORTC trial demonstrated more favorable outcomes in patients treated with radical nephrectomy (during a median follow-up period of 9.3 years, 25 % of patient treated with partial nephrectomy died versus 18.3 % treated with radical nephrectomy) [15]. However, in the targeted population of patients with proven RCC, the mortality trend in favor of radical nephrectomy was not significant. This study has been widely criticized due to problems with accrual, premature study termination, and crossover of patients from the partial to radical nephrectomy arm. Thus, interpretation of this study is not clear and currently, partial nephrectomy remains the first line treatment for localized RCC < 4 cm given similar oncological outcomes overall between partial and radical nephrectomy [8, 9].

Partial nephrectomy may be performed in the conventional open manner or utilizing laparoscopic or robot-assisted laparoscopic techniques. Despite minor differences in techniques, the goal of partial nephrectomy is to achieve complete tumor removal with a negative margin in an efficient manner such that ischemia times are kept to a minimum and consequent renal damage is minimized. Importantly, warm ischemia time during partial nephrectomy is a critical variable that must be minimized; each minute of warm ischemia time is associated with a 6 % greater risk of acute kidney injury and a 4 % greater risk for stage 4 CKD, with ischemia times less than 25 min being ideal [16]. Novel "no ischemia" techniques are also available and may have superior renal function preservation effects [17].

Another less invasive option for T1a RCC and in particular tumors <3 cm is percutaneous probe ablation [18]. This is most commonly in the form of radiofrequency ablation or cryotherapy [18]. Given that this procedure is percutaneous and generally performed as an outpatient procedure, it is particularly beneficial for the older and/or patients with significant comorbid conditions. Percutaneous techniques are most effective in treating tumors < 3 cm located a distance from major vessels [19]. Success rates for percutaneous probe ablation are slightly inferior to that of partial nephrectomy, but considered acceptable at > 90 % recurrence-free rates (rates vary depending on the study population and definition of failure) [19–22].

More recently, there is a growing experience with percutaneous renal tumor biopsy and active surveillance for small renal masses [23–26]. In centers with experience, the diagnostic rates of renal tumor biopsy are > 80 % with a very low complication rate (< 5 %) and importantly, a benign histology rate of > 25 % [23, 24]. Given that upwards of 25 % of solid enhancing small renal masses are benign, some have adopted the practice of performing a biopsy on all small, localized lesions before surgical treatment. Furthermore, a large prospective series demonstrated an average growth of small renal masses of 0.13 cm/year and local progression or metastases were extremely rare in these series [25, 26]. Active surveillance for T1a RCC is now

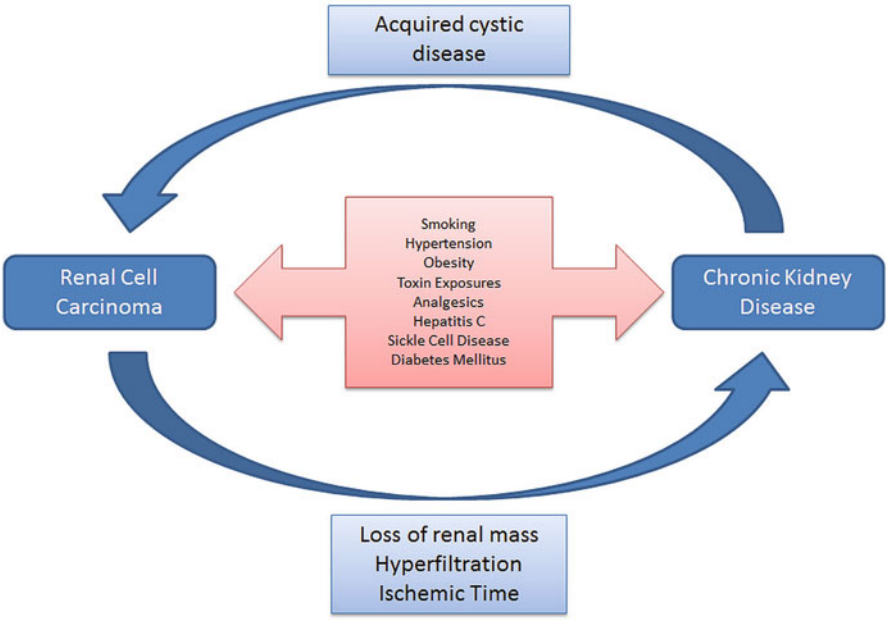

Fig. 10.1 Bidirectional interactions between CKD and RCC

an acceptable treatment option in older and/or patients with significant comorbid medical conditions.

CKD in the Patient with RCC

Given the age and comorbid conditions in the patient population with RCC, it is not surprising that 25 % of these patients have concomitant CKD prior to tumor nephrectomy (Fig. 10.1) [27]. Many of the risk factors for RCC overlap with those for CKD such as hypertension, smoking, obesity, analgesic use, chronic hepatitis C infection, diabetes mellitus, and others [28]. In fact, approximately 10 % of tumor nephrectomy specimens demonstrate features of diabetic nephropathy, 2–9 % may have focal segmental glomerulosclerosis, and another 20 % show hypertensive nephrosclerosis [29, 30]. Importantly, not only is CKD more prevalent in the population with RCC but the risk of developing RCC has also been estimated to be 30 times greater in CKD patients with acquired cystic disease of the kidney than in the general population [31]. Acquired cystic disease develops in approximately 35–50 % of patients with advanced CKD, approximately 6 % who eventually develop RCC [32]. This bidirectional risk between CKD and renal cell carcinoma is depicted in Fig. 10.1.

For those patients with mild CKD or no evidence of CKD prior to the diagnosis of RCC, the surgical procedure will have important effects on long-term renal function. Most studies support the fact that there will be clear differences in resultant glomerular filtration rate (GFR) between partial and radical nephrectomies, both in the short- and long-term. For example, Huang et al. reported that the probability of being free from a GFR < 60 ml/min/1.73 m^2 at 5 years post procedure was 67 % and 23 % for partial and complete nephrectomy, respectively with no difference in oncologic efficacy [27]. Another large population-based study of 1151 patients who had undergone tumor nephrectomy reported that 10.5 % of this group had adverse renal outcomes over a 32-month follow-up (including ESKD, need for acute dialysis, rapidly progressive CKD, and stage 4 or worse CKD) [33]. In this study, radical nephrectomy had a hazard ratio of 1.75 (95 % confidence interval 1.02–2.99) for these adverse renal outcomes as compared to partial nephrectomy [33]. A study in the Medicare population of patients with T1a RCC demonstrated that patients who underwent radical nephrectomy had a higher rate of CKD than partial nephrectomy patients (20 vs. 11 %) and the 5-year freedom from new onset CKD was 82 % for those undergoing radical nephrectomy versus 91 % for those undergoing partial nephrectomy [34]. A dissenting study is that from the EORTC, where compared with radical nephrectomy, nephron sparing surgery substantially reduced the incidence of at least moderate renal dysfunction (eGFR < 60), although with available follow-up the incidence of advanced kidney disease (eGFR < 30) was relatively similar in the two treatment arms, and the incidence of kidney failure (eGFR < 15) was nearly identical [15].

Given the known association of CKD with increased mortality, especially from cardiovascular disease it might be surmised that surgical approaches which achieve better long-term renal function while maintaining oncological cure rates would be associated with improved overall outcomes [35]. However, the data supporting better long-term outcomes with nephron sparing surgery over radical nephrectomy remain controversial and require further study. Many of the studies supporting improved outcomes with nephron-sparing surgery are single institution retrospective cohorts with selection bias and residual confounding. The only randomized trial, from the EORTC, did not find a survival advantage of partial versus radical nephrectomy [15]. However, a recent pooled analysis of 41,010 patients demonstrated that partial nephrectomy was associated with a 61 % risk reduction in developing CKD and 19 % risk reduction for all-cause mortality [36]. More research is needed to elucidate whether the anticipated consequences of preserving renal function translate into improved nonrenal, non-oncological outcomes.

Diagnosis of Subclinical CKD from the Tumor Nephrectomy Sample

The pathologic evaluation of tumor nephrectomy specimens has traditionally focused entirely on the renal mass with many parameters that must be analyzed and reported for every carcinoma, including size, Fuhrman grade, margin status, capsule or renal

vein invasion, and other features. This focus has meant that the opportunity to diagnose noncancer kidney disease may be lost. In fact, approximately 60–88 % of such background diagnoses are not identified during the initial nephrectomy evaluation [29, 30]. A recent European survey of genitourinary pathologists revealed that over 25 % do not evaluate the nonneoplastic kidney parenchyma even though a portion of the tissue is properly sampled for every specimen [37]. In order to address these concerns, a modification of the College of American Pathologist kidney cancer protocol and checklist form was made to include reporting of nonneoplastic, contiguous disease [38]. Given that the majority of renal masses are stage 1 tumors with excellent outcomes, the status of the nonneoplastic kidney parenchyma is a critical pathologic parameter as it may discover previously unrecognized kidney pathology and aid postsurgical care. The further importance of finding renal parenchymal abnormalities is that those patients with these findings had a greater rise in serum creatinine levels postsurgery as compared to those with normal renal tissue ($1.1 +/- 1.8$ mg/dL vs. $0.2 +/- 0.2$ mg/dL, $p = 0.01$) [39]. Other studies have also demonstrated that findings of renal parenchymal abnormalities in the nonneoplastic tissue were useful in predicting longer term kidney function [40, 41].

Post-Nephrectomy Follow-up Care

Given the fact, that more patients are surviving with RCC and that CKD is common as the population ages, it follows that nephrologists will have an increasing role in the care of these patients. However, the nature of this role is unclear. As described above, CKD has been noted to be a common complication of nephrectomy for RCC. However, the move to nephron sparing surgery will hopefully diminish the likelihood of there being a large reduction in GFR following kidney cancer surgery and thus also lessen the burden of subsequent CKD. This may be offset by other factors such as the increasing prevalence of RCC as well as the older age of the population undergoing treatment for RCC. Furthermore, if pathologists consistently review nonneoplastic renal tissue, previously undiagnosed renal parenchymal diseases may be discovered which require nephrology evaluation and possibly therapy.

Thus, prudent recommendations for nephrology evaluation for the patient with RCC include the following: (1) the finding of any renal parenchymal pathological process on evaluation of noncancerous kidney tissue (such as previously undiagnosed glomerular or interstitial disease or significant (> 30 %) fibrosis) and (2) postoperative eGFR (once renal function is stable) < 60 ml/min. Furthermore, those patients with preoperative eGFRs < 60 ml/min would also benefit from nephrology consultation prior to surgery with close monitoring of postoperative kidney function.

In aggregate, data support a benefit of partial nephrectomy over radical nephrectomy for stage 1 renal carcinomas. Renal function is better preserved, oncological outcomes are not jeopardized, and overall mortality may be improved. Furthermore, data support having pathologists comment on the nonneoplastic renal tissue in the

tumor nephrectomy specimen as these findings can help predict subsequent falls in GFR. There is an urgent need for communication between the nephrologist, urologist, and pathologist in deciding the right surgical and postoperative course of action for RCC.

Case #1 Follow-up and Discussion

The case described at the beginning of this chapter demonstrates the bidirectional nature of CKD–RCC interactions. This patient had shared risk factors for both diseases and in fact, had significant stage 3 CKD prior to nephrectomy that was not appreciated. Ten percent of tumor nephrectomy specimens demonstrate features of diabetic nephropathy; 2–9 % may have focal segmental glomerulosclerosis and another 20 % show hypertensive nephrosclerosis [29, 30]. His tumor nephrectomy specimen substantiated the findings of CKD along with features of hypertensive nephrosclerosis (correct answer to the question is c) and would predict a more rapid deterioration of kidney function postoperatively, which, in fact, was observed. More likely, a partial nephrectomy in this patient would have resulted in the oncologic cure but led to greater preservation of kidney function. This highlights the need for communication between the nephrologist, urologist, and pathologist in deciding the right surgical and postoperative course of action.

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Chapter 11
Renal Disease Following Hematopoietic Stem Cell Transplantation

Rimda Wanchoo and Albert Q. Lam

List of Abbreviations

AKI	Acute kidney injury
BMT	Bone marrow transplant
CKD	Chronic kidney disease
ESKD	End-stage kidney disease
GFR	Glomerular filtration rate
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplant
HUS	Hemolytic uremic syndrome
NS	Nephrotic syndrome
SOS	Sinosoidal obstruction syndrome
TBI	Total body irradiation
TMA	Thrombotic microangiopathy
TPA	Tissue plasminogen activator
TPE	Therapeutic plasma exchange
TTP	Thrombotic thrombocytopenic purpura
VEGF	Vascular endothelial growth factor
VOD	Veno-occlusive disease

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Overview of Hematopoietic Stem Cell Transplantation Protocols

Hematopoietic stem cell transplant (HSCT) is the only cure for a variety of hematologic and oncologic diseases. Despite the increasing number of transplants performed worldwide, renal complications that develop during the peri- and post-transplant period lead to significant morbidity and mortality. The risk of kidney injury following HSCT varies with the conditioning regimen [1]. HSCT can be broadly classified into autologous and allogeneic transplant. *Autologous transplants* involve harvesting a patient's own bone marrow or peripheral stem cells before high-dose myeloablative therapy followed by reinfusion. The harvested cells are usually frozen at temperatures below − 120 °C and used within a few weeks. Autologous transplantation does not induce graft versus host disease (GVHD) and can be performed in older patients. Mortality in autologous transplantation is lower compared with allogeneic transplantation, but the absence of graft versus tumor activity reduces its effectiveness. The contamination of grafts with tumor cells also contributes to relapse in hematologic cancers [2]. *Allogeneic transplantation* involves harvesting cells from a related or unrelated donor. Due to the establishment of large registries for bone marrow donors and cord blood, the chances of finding a match in allogeneic transplants have greatly increased. Allogeneic grafts initiate an immune reaction related to histocompatibility. The severity of the reaction depends on the degree of incompatibility that in turn is determined by a complex biology in which class I and class II HLA cell surface glycoproteins present peptides from a degraded protein. Recipient T lymphocytes recognize donor antigens and reject grafts [1]. Allogeneic transplants come with a risk of GVHD, but are also associated with lower rates of malignant relapse owing to an immune-mediated graft versus host effect [3]. The infusion of hematopoietic stem cells is usually preceded by either myeloablative therapy (combination of chemotherapy or chemotherapy plus total body radiation) or non-myeloablative (reduced intensity) conditioning. Myeloablative conditioning (autologous or allogeneic) regimens are associated with significant morbidity during the cytopenic intervals and are usually administered to younger patients without comorbidities. Non-myeloablative (allogeneic only) regimens are typically reserved for older patients or those with significant comorbid conditions. This therapy allows the host hematopoietic cells to coexist with donor stem cells to achieve mixed hematopoietic cell chimerism [4].

Case #1

A 67-year-old Caucasian man with peripheral T-cell lymphoma has failed treatment with cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone (CHOP) and is admitted for an autologous hematopoietic stem cell transplant (HSCT). His conditioning regimen consists of high-dose cyclophosphamide, BCNU, and VP-16 (CBV conditioning), which he tolerates well. He receives his stem cell transplant without any complications. However, on day

8 following his stem cell infusion, he develops a rapid rise in his serum total and direct bilirubin levels, accompanied by increasing peripheral edema, abdominal ascites, and weight gain. What is the most likely explanation for his symptoms?
a. Portal vein thrombosis
b. New onset cirrhosis of the liver
c. Sinusoidal obstruction syndrome
d. Congestive heart failure

Acute Kidney Injury

The risk of acute kidney injury (AKI) in HSCT varies based on the type of HSCT performed. Autologous HSCT has the lowest risk of moderate-to-severe AKI and AKI requiring renal replacement therapy. Non-myeloablative allogeneic HSCT has slightly higher risk, however the highest risk of AKI and AKI necessitating dialysis is seen in myeloablative allogeneic transplantation. Table 11.1 summarizes the risk and mortality associated with the different forms of HSCT [5, 6].

The incidence of AKI after autologous HSCT ranges from 15 to 20 % [6–8]. The low incidence can be explained by the absence of GVHD, and therefore less use of calcineurin inhibitors. In addition, since engraftment occurs sooner, the time for which patients remain cytopenic is shorter, leading to a lower risk of sepsis and antibiotic exposure that can lead to AKI [8].

The risk factors for AKI in myeloablative transplantation are listed in Table 11.2 [9, 10]. Regardless of the setting of AKI, the degree of renal failure correlates with mortality [11, 12]. A meta-analysis of HSCT patients with AKI showed that AKI was independently associated with a twofold increase in mortality, which is even higher when dialysis therapy is required [11]. When AKI occurs in the first 100 days of the transplant, the mortality is higher, especially in the setting of non-myeloablative HSCT [11–14].

Table 11.1 Types of HSCT and renal complications (based on references [9–12,14])

Type of conditioning	Donor relationship	CNI exposure	Risk of GVHD	Risk of AKI (%)	Risk of AKI requiring RRT (%)	Risk of Mortality if RRT (%)
Myeloablative	Allogeneic	High	Very high	59	17	> 80
Non-myeloablative	Allogeneic	High	High	39	4	> 80
	Autologous	None	None	18	4	70

AKI acute kidney injury, *CNI* calcineurin inhibitors, *GVHD* graft versus host disease, *RRT* renal replacement therapy

Table 11.2 Risk factors associated with AKI following HSCT (based on references [5, 6, 9, 13])

Amphotericin B exposure
Early weight gain > 2 kg
Jaundice
Pre-transplant serum creatinine > 0.7 mg/dl
Veno-occlusive disease
GVHD grade 3–4
Sepsis
Lung toxicity
Acyclovir exposure
Calcineurin inhibitor exposure
Admission to intensive care unit

The most common causes of AKI after HSCT are sepsis, hypotension, and nephrotoxic antibiotics administered during the cytopenic interval [5]. Tumor lysis syndrome is rare but can be seen as an early cause of AKI following certain conditioning regimens. Prerenal insult from vomiting and diarrhea is not uncommon. Common nephrotoxins used in HSCT patients include methotrexate, amphotericin B, aminoglycosides, intravenous contrast, angiotensin-converting enzyme inhibitors, calcineurin inhibitors, and acyclovir [13].

Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD) of liver, is a serious complication following HSCT. The pathogenesis of SOS has been attributed to damage to hepatic sinusoids, and it typically presents with tender hepatomegaly, jaundice, fluid retention and weight gain, and hyperbilirubinemia following high-dose myeloablative conditioning therapy [15]. SOS occurs relatively early after HSCT, generally within the first 30 days. While the reported prevalence of SOS has ranged from 5 to 60 % of patients, the overall mean incidence of SOS is approximately 14 % [16]. SOS occurs more frequently after myeloablative allogeneic HSCT than after autologous HSCT and rarely occurs with non-myeloablative HSCT [17]. A number of risk factors for developing SOS have been identified, including preexisting liver disease [17], choice of conditioning regimens (particularly those including busulfan, cyclophosphamide, or total body irradiation) [17, 18], older age, certain medications (methotrexate, itraconazole, sirolimus, and norethisterone) [19–21], and an underlying diagnosis of osteopetrosis, primary hemophagocytic lymphocytosis, or adrenoleukodystrophy [15, 22].

Case #1 Follow-up and Discussion:
This patient shows signs and symptoms of sudden-onset portal hypertension following HSCT. Shortly after the onset of this presentation, an abdominal ultrasound with duplex sonography is performed, demonstrating reversal of

portal venous flow. The patient is given a diagnosis of sinusoidal obstruction syndrome. The Correct Answer Is c.

Case #2
On day 16 post transplant, the serum total and direct bilirubin levels of the patient in the Case #1 are now 31.3 mg/dL (normal range 0–1.0 mg/dL) and 23.1 mg/dL (normal range 0–0.3 mg/dL), respectively. His weight has increased by 9 kg since admission. His nurse reports that he now appears more lethargic and is unable to answer questions appropriately. His daily urine output has begun to decrease from approximately 1.5 L to 400 mL, and his serum creatinine level has risen from a baseline of 0.9 mg/dL to 1.4 mg/dL in the past 24 h. Which diagnostic test finding would most likely be seen in this patient?

a. The presence of red blood cell casts in the urine sediment
b. A low fractional excretion of sodium
c. Blood cultures positive for *Escherichia coli*
d. A renal ultrasound demonstrating moderate bilateral hydronephrosis

AKI occurs to some extent in all patients with SOS, with as many as 50 % of patients developing severe AKI [23] and half of these requiring dialysis [24]. Patients with SOS-associated AKI present in a manner that is nearly identical to the hepatorenal syndrome. Early symptoms include sodium retention, peripheral edema, ascites, and weight gain, accompanied by liver dysfunction and hyperbilirubinemia. The onset of AKI, which typically ensues 10–16 days post HSCT, may be slow and progressive, and may be triggered by factors such as hypotension, sepsis, or exposure to nephrotoxic agents. Oliguria may be present, accompanied by a persistently low fractional excretion of sodium. Urinalysis with sediment is often bland but may sometimes reveal granular casts in patients who progress to developing tubular injury from hypotension or nephrotoxic agents. Evidence of intrinsic kidney lesions has not been seen on kidney biopsies or autopsies from patients with SOS, consistent with the understanding that SOS-associated AKI is most likely hemodynamic in pathophysiology [24]. Mortality rates with severe AKI are high, approaching 40 and 85 % in patients with a doubling of serum creatinine and those requiring dialysis, respectively [25].

Case #2 Follow-up and Discussion:
This patient, as a consequence of his sinusoidal obstruction syndrome, has developed prerenal azotemia, secondary to hepatorenal-like physiology. His urine sodium level is nearly undetectable and his fractional excretion of sodium is < 1 %, consistent with his kidneys being in a sodium-avid state. The Correct Answer Is b.

While the mortality is high in patients with SOS and moderate-to-severe AKI, more than 70 % of patients with SOS recover with supportive management [15]. Upon diagnosis of SOS, prompt measures should be taken to maintain sodium and water balance, preserve renal blood flow, and manage peripheral edema and ascites with the judicious use of diuretics and therapeutic paracenteses as needed. In patients with large fluid intake requirements, fluid management can be particularly challenging, and renal replacement therapy may be necessary. In these circumstances, continuous modalities may be preferred.

Defibrotide is a single-stranded oligodeoxyribonucleotide with antithrombotic, profibrinolytic, and anti-ischemic properties, which has shown efficacy in the treatment and prevention of SOS [26–32]. Its use in severe SOS was first reported by Richardson and colleagues in 1998 in a compassionate use study of 19 patients, 8 of whom had resolution of SOS when treated with doses ranging from 5 to 60 mg/kg/day [33]. Phase II studies performed by the same group randomized adult and pediatric patients with SOS to lower dose (25 mg/kg/day) versus higher dose of (40 mg/kg/day) defibrotide every 6 hours for 14 days or until complete remission, progression of SOS, or severe toxicity was seen. The complete remission rate was 46 %, and no significant difference was found between the two doses [29]. Phase III studies are currently underway to evaluate the efficacy of defibrotide in both treatment and prevention of SOS. The main adverse effects of defibrotide include hemorrhage and hypotension.

Other agents used in the treatment of SOS with varying success include tissue plasminogen activator (TPA) and methylprednisolone. Infusion of heparin and/or ursodeoxycholic acid administered immediately before induction therapy may also be moderately successful as preventive measures.

Epidemiology and Incidence of Chronic Kidney Disease

The incidence of chronic kidney disease (CKD) after HSCT is variable and ranges from 13 to 66 % in adult studies [34–37]. The diagnosis of CKD in an HSCT patient is of great significance as these patients are at a higher risk of mortality despite being controlled for other comorbidities. The mortality is close to 90 % in patients who progress to end-stage renal disease and require dialysis [38]. Hingorani and colleagues demonstrated that the increased risk of CKD was associated with AKI post HSCT, as well as the presence of acute or chronic GVHD [39]. The authors suggest that the kidney is either a target organ of GVHD via a T cell-mediated process or an innocent bystander affected by the systemic inflammatory and cytokine cascade induced by GVHD. In animal models of GVHD, tissue destruction in acute GVHD does not require alloantigen expression on target epithelial cells for cellular toxicity and can be mediated by inflammatory cytokines [40]. The growth in the use of non-myeloablative protocols may also lead to an increase in prevalence of kidney disease as older patients with more comorbidities are getting transplanted. Another cause of CKD is the long-term exposure to calcineurin inhibitors.

For the purpose of this review we divide CKD post HSCT as:

1. ***Nephrotic syndrome***
2. ***Thrombotic microangiopathy***
3. ***Chronic calcineurin inhibitor nephrotoxicity***
4. ***Viral infections and renal disease***
5. ***Idiopathic CKD***

Case #3
A 65-year-old male with a history of acute myelogenous leukemia for which he underwent a matched unrelated non-myeloablative HSCT 4 years ago is referred for nephrotic syndrome. His spot urine protein to creatinine ratio is consistent with 23 g of protein in 24 hours, and his serum albumin is 2 g/dL. His serum creatinine is stable at 1 mg/dL. A kidney biopsy is performed. Figure 11.1 shows the electron microscopy findings. The most likely diagnosis is:

a. Membranous nephropathy
b. Minimal change disease
c. IgA nephropathy
d. Focal segmental glomerulosclerosis

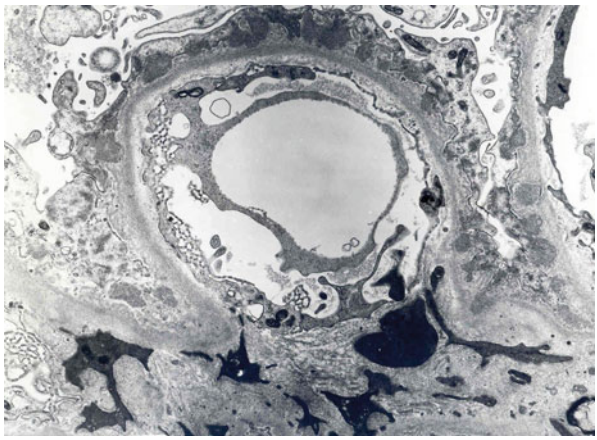

Fig. 11.1 Electron microscopy reveals electron-dense subepithelial deposits

Nephrotic Syndrome

There have been several case reports and case series of nephrotic syndrome (NS) developing post HSCT. The common histological lesions seen when these patients are biopsied are membranous nephropathy followed by minimal change disease.

The two largest series in the literature describing NS after allogeneic HSCT are from Reddy and Terrier [41, 42].

Animal models of chronic GVHD describe the kidneys as a target organ with histopathological features of membranous nephropathy [43], however renal involvement in humans with chronic GVHD is not well established. A review of literature by Brukamp et al. [44] revealed a close temporal relationship between the development of NS shortly after cessation of immunosuppression and the diagnosis of chronic GVHD. The authors in this review support the existence of renal GVHD manifesting as NS clinically. When biopsied, 61 % of these patients had a membranous pattern of glomerular renal injury and 22 % had minimal change disease. Less common were focal segmental glomerulosclerosis and proliferative glomerulonephritis. It is proposed that chronic GVHD may precipitate glomerular disease via a complex donor T cell and host antigen-presenting cell interaction, or alternatively the donor stem cells may modulate disease activity of glomerulonephritis by means other than GVHD [44].

The pathophysiology of idiopathic membranous nephropathy has been linked to antibodies against the phospholipase A2 receptor (PLA2R), M type, expressed on podocytes. In a study recently published by Huang et al. [45], the clinical course of five patients was followed after HSCT. All five had biopsy-proven membranous nephropathy and evidence of chronic GVHD that was in remission. Of the five patients, four tested negative for anti-PLA2R antibodies, suggesting that the pathogenesis of HSCT-related membranous nephropathy may be different from that of idiopathic membranous nephropathy.

In the largest series published to date [46] consisting of retrospective analysis of 95 cases of HSCT-associated NS, the authors argue against chronic GVHD as a contributor to the pathogenesis of HSCT-associated glomerular diseases. In their study they noted that although chronic GVHD was common among the HSCT recipients with glomerular disease (72 %), this was no different from that observed in the overall HSCT population. Furthermore, their study showed no statistically significant association between cessation of immunosuppressive medication and onset of glomerular disease. A substantial number of patients (40 %) in this series developed glomerular disease while on immunosuppressive medication, and nearly a third of the patients were diagnosed with glomerular disease in the absence of concomitant GVHD. Similarly, a study from the National Institutes of Health reported a high incidence of NS in a cohort of 163 patients undergoing non-myeloablative HSCT from related HLA-compatible donors. About 7 of the 163 patients developed NS (four with membranous nephropathy), whereas no incident cases were reported in the myeloablative group. Thus, the authors did not find an association of GVHD with glomerular disease [47]. Of note, glomerular disease also develops in recipients of autologous HSCT, a setting in which GVHD cannot be explained as a possible pathogenic mechanism.

Minimal change disease is the second most common pathological diagnosis seen in HSCT recipients. In addition to this being a manifestation of glomerular injury related to GVHD or mediated by cytokines, recurrence of the primary malignancy (i.e., lymphoma) for which the patient underwent a stem cell transplant should be considered. In a case report of NS diagnosed as minimal change disease, there was

increased production of TNF-alpha and IFN-gamma by the donor T cells with lack of cellular infiltrate, which suggested that the glomerular injury was secondary to cytokine production and stimulated by alloantigen in an extrarenal site [48].

Currently, no conclusion can be drawn on the pathogenesis of NS post HSCT. It seems likely this is a renal manifestation of chronic GVHD, although based on the current evidence there remain some unanswered questions, and more research is needed in this area.

Case # 3 Follow-up and Discussion:
The electron microscopy demonstrates subepithelial deposits typical of membranous nephropathy. Anti-phospholipase A2 receptor antibodies were negative in the serum and it was assumed that the patient had GVHD-associated membranous nephropathy and was started on immunosuppressive agents. The Correct Answer Is a.

Case #4
A 45-year-old Caucasian man with acute myelogenous leukemia is treated with cytarabine and daunorubicin ("7 + 3") as induction chemotherapy prior to undergoing a mismatched related donor hematopoietic stem cell transplant from his younger brother. His conditioning regimen consists of cyclophosphamide and total body irradiation. He is started on prophylaxis against graft versus host disease (GVHD) with tacrolimus and sirolimus. Upon discharge from the hospital, his serum creatinine is 1.0 mg/dL. One month after his transplant, his creatinine increases to 2.3 mg/dL, accompanied by new-onset thrombocytopenia and elevated serum lactate dehydrogenase level. A few schistocytes are observed on his peripheral smear. His blood pressure has worsened in the interim as well. Which of the following etiologies best explains this patient's acute kidney injury?

a. Volume depletion
b. Chronic graft versus host disease with renal involvement
c. Thrombotic microangiopathy
d. Cytarabine-associated nephrotoxicity

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA), also known as bone marrow transplant nephropathy or radiation nephropathy, is a common cause of AKI in the HSCT patient. Prevalence rates in the literature have ranged widely from 0.5 to 76 %, though

large retrospective studies have reported prevalence rates of 10–25 % [49]. HSCT-associated TMA can occur with both allogeneic and autologous HSCT [50, 51] and typically has an onset 20–99 days post transplant [52]. HSCT-associated TMA can present similarly to hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) with anemia, thrombocytopenia, and renal insufficiency. The kidney is the most commonly affected organ, and injury outside the kidney is relatively rare but has been reported [49]. Though most patients have a mild form of disease that often leads to the development of CKD [53], a subset of patients present with a more severe form of TMA that is associated with high mortality [54]. Hypertension is often present. Patients usually have evidence of low-grade hemolysis with an elevated serum lactate dehydrogenase (LDH) level, low serum haptoglobin, and the presence of schistocytes on peripheral smear. Analysis of the urine may reveal hematuria and/or proteinuria or may be normal, and the urine sediment can also vary from being relatively bland to showing cellular casts.

The pathogenesis of HSCT-associated TMA, though not clearly understood, has been attributed to renal endothelial cell injury [55]. Multiple mechanisms of endothelial damage in the setting of HSCT-associated TMA have been proposed. One primary cause of renal endothelial damage is the HSCT conditioning regimen. Both myeloablative and reduced-intensity conditioning regimens—especially those employing busulfan, fludarabine, platinum-based agents, and total body irradiation (TBI)—have been shown to be risk factors for the development of HSCT-associated TMA [56–58]. An association between TBI and TMA has been suggested by studies in animals and humans which demonstrate that (1) the clinical presentation and histopathological features of HSCT-associated TMA are nearly identical to those seen in radiation nephritis, (2) the delayed onset of HSCT-associated TMA is similar to that of acute radiation nephritis following radiation exposure, (3) partial renal shielding during TBI decreases the incidence of HSCT-associated TMA from 26 to 6 %, and (4) fractionation of the radiation dose appears to reduce the risk of HSCT-associated TMA [24, 59–61] Recent retrospective data have also shown a correlation between TBI > 1200 cGy and HSCT-associated TMA [53]. While strategies to reduce radiation injury can be employed, they may decrease the efficacy of tumor cell eradication [24]. The next chapter in this book discusses radiation nephropathy in further detail.

Infections by a variety of pathogens, including *Aspergillus*, cytomegalovirus, adenovirus, parvovirus B19, human herpes virus-6, and BK virus, have also been linked to HSCT-associated TMA [49, 53, 62, 63]. Patients with viremia have been found to have increased levels of thrombomodulin, plasminogen activator inhibitor (PAI-1), and inflammatory cytokines—factors which may promote the development of TMA [49, 64]. Calcineurin inhibitors such as cyclosporine and tacrolimus are known to cause endothelial injury and TMA through several mechanisms, including direct cytotoxic damage, platelet aggregation, elevation in the levels of von Willebrand factor and thrombomodulin, alteration in proteins regulating complement pathways, and reduction in prostacyclin and nitric oxide production [49]. The addition of sirolimus to a calcineurin inhibitor may increase the risk of HSCT-associated TMA, possibly by impairing the repair of damaged endothelium or decreasing the local production

of vascular endothelial growth factor (VEGF) [55]. *GVHD* in HSCT patients has also been shown to be associated with TMA, with mechanisms such as circulating inflammatory cytokines, direct endothelial cell injury from cytotoxic donor T lymphocytes, activation of coagulation pathways, and reduced levels of VEGF contributing to the development of endothelial damage [53]. While it has been proposed that HSCT-associated TMA may represent a form of renal or endothelial GVHD, there is no compelling evidence supporting this hypothesis. A role for abnormal activation of the *complement system* in HSCT-associated TMA, as is the case in atypical HUS, has also been proposed. The small studies that have examined the question of implicating a role for abnormal activation of the complement system in HSCT-associated TMA are limited by their size but have not demonstrated any abnormalities in measured complement levels or directly sequenced complement genes in patients with HSCT-associated TMA [56, 65]. Interestingly, however, antibodies against complement factor H (CFH) have been detected in patients with HSCT-associated TMA [44, 66]. More studies are required to further elucidate the role of alloantibodies and the complement system in the pathogenesis of HSCT-associated TMA.

Establishing the diagnosis of HSCT-associated TMA can often be challenging. The diagnosis of TMA is made on the basis of characteristic pathological findings seen on kidney biopsy, including glomerular endothelial swelling, basement membrane duplication, mesangiolysis, occluded vascular lumens, and tubular injury with interstitial fibrosis [67]. However, because of the increased risk of bleeding in the HSCT patient, kidney biopsies are rarely performed unless there are atypical features in the presentation. Clinical criteria for the noninvasive diagnosis of HSCT-associated TMA have been proposed by two separate groups in an attempt to standardize the diagnosis [62, 68] (Table 11.3). Follow-up validation studies, however, have revealed limitations to the use of these criteria [53, 63, 69]. Autopsy studies have found pathologic evidence of HSCT-associated TMA in patients who did not meet criteria for clinical diagnosis [70, 71], further highlighting the difficulty of establishing reliable guidelines for the diagnosis of HSCT-associated TMA. In light of these challenges, clinicians evaluating HSCT patients should be attentive to the development of renal manifestations, such as hypertension and proteinuria, which may herald an early diagnosis of HSCT-associated TMA.

Management of HSCT-associated TMA is primarily supportive. Calcineurin inhibitors are frequently discontinued, but this may present a challenge to patients who require these medications for treatment of significant GVHD. Alternative agents that can be used to substitute for calcineurin inhibitors include corticosteroids, mycophenolate mofetil, daclizumab (humanized monoclonal antibody to the alpha chain of the IL-2 receptor), rituximab, and defibrotide [49, 72, 73]. Blood pressure control is important, and preclinical data suggest that angiotensin-converting enzyme inhibitors may be useful in treating HSCT-associated TMA [74]. Therapeutic plasma exchange (TPE) has been used to treat HSCT-associated TMA with variable success, though the mechanism and rationale for its benefit are unclear. In reviewing 11 studies from 1991 to 2003, Ho and colleagues reported a median response rate of 36.5 % and associated mortality rate of 80 % in patients treated with TPE [62]. A summary of more recent studies demonstrated response rates ranging from 27 to

Table 11.3 Clinical criteria for the diagnosis of HSCT-associated TMA

BMT CTN Toxicity Committee consensus definition [33]	International Working Group definition [39]
RBC fragmentation and ≥ 2 schistocytes per high-power field on peripheral smear	All of the following present: Increased percentage (4 %) of schistocytes in peripheral blood
Concurrent increased serum LDH above institutional baseline	
	De novo, prolonged, or progressive thrombocytopenia (platelet count $< 50 \times 10^9$/L or ≥ 50 % decrease from prior levels)
Concurrent renal[a] and/or neurologic dysfunction without other explanations	
Negative direct and indirect Coombs test results	Sudden and persistent increase in LDH
	Decrease in hemoglobin concentration or increased red blood cell transfusion requirement
	Decrease in serum haptoglobin concentration

[a]Doubling of serum creatinine from baseline (baseline = creatinine before hydration and conditioning) or 50 % decrease in creatinine clearance from baseline

80 %, though the authors note that these studies included uncontrolled, heterogeneous patient populations [49]. Of these, the only prospective study to evaluate the benefit of TPE showed a response rate of 64 % in 11 patients who underwent both cyclosporine withdrawal and treatment with TPE [57]. Based on these collective data, there is still no clear evidence of benefit supporting the use of TPE as standard of care. A number of experimental agents for the treatment of TMA are under investigation, including 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, prostacyclin analogs, endothelin receptor antagonists, antithrombin III, IgG, and anti-TNF agents [49, 73].

Case #4 Follow-up and Discussion:
This patient's presentation is consistent with HSCT-associated thrombotic microangiopathy. The constellation of findings of hemolysis, renal insufficiency, hypertension, and non-nephrotic proteinuria suggests thrombotic microangiopathy. Cytarabine-associated nephrotoxicity is not known. The Correct Answer Is c.

Case #5
A 45-year-old male with acute myelogenous leukemia undergoes a myeloablative hematopoietic stem cell transplant. His post-transplant course is significant for hepatic sinusoidal obstruction syndrome (SOS), which is treated appropriately. He is admitted 2 months later with fever, hematuria, flank pain, and acute kidney injury. He admits to taking ibuprofen for flank pain. A kidney biopsy is performed (see Fig. 11.2).

The most likely diagnosis is:

a. Adenovirus nephritis
b. Acute tubular necrosis
c. NSAID-induced acute interstitial nephritis

Viral Infections and Kidney Diseases

The two common viral infections associated with renal disease in HSCT recipients are BK virus and adenovirus. Both the viruses are well known to cause hemorrhagic cystitis.

Adenovirus

The incidence of systemic adenovirus infection in HSCT patients is variable, ranging from 5 to 29 % [75, 76]. The infection can occur as a result of primary infection, reactivation of a latent infection, or transmission with a transplanted organ. Isolation of adenovirus from more than one site correlates with increased risk of invasive disease. Kidney biopsy in adenovirus infection shows interstitial nephritis with the presence of viral inclusions in tubular cells. Figure 11.2 shows light microscopy findings of adenovirus nephritis. Presence of granulomas around the tubules is quite specific. Necrotizing tubulointerstitial nephritis is associated with significant mortality. In a study published by Bruno et al. [77], adenovirus nephritis was diagnosed in 21 HSCT patients (19 by autopsy and 2 by biopsy). They identified the presence of GVHD as a risk factor. Adenovirus nephritis led to renal failure in 90 % of the infected patients and in about 78 % of these patients adenoviruria was also present. Also associated with adenovirus is ureteral obstruction leading to hydronephrosis [78, 79].

BK Virus

BK viruria has been reported in 50 % of patients after HSCT within 2 months of transplantation [80–83]. Hemorrhagic cystitis commonly associated with BK infection has been found in 10–25 % of recipients. Mostly, a primary infection with the

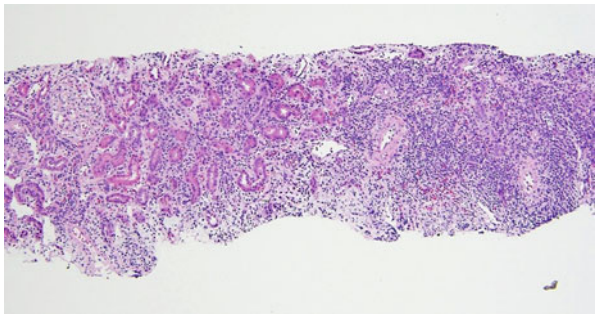

Fig. 11.2 Low-power light microscopy showing interstitial inflammation

virus occurs in early childhood followed by BK virus establishing latency in the genitourinary tract. Suppression of the immune system leads to reactivation of the virus which commonly manifests as viruria, however in a small proportion of patients there is progression to invasive infection of the kidney, namely polyomavirus nephropathy [84, 85] There have been reports published in the literature of tubulointerstitial nephritis developing secondary to polyomavirus in native kidneys of nonrenal transplant patients [86, 87] A report published on children showed that the severity of the renal damage secondary to BK virus was dependent on the BK viral load. Patients with BK viral load > 10,000 copies/mL had a more severe manifestation of the disease requiring aggressive treatment, including dialysis with survival of 58 % at 1 year. In contrast, patients with lower levels < 10,000 copies/mL had less severe disease with an improved survival of 89 % at 1 year [88].

The definitive diagnosis for BK nephropathy is kidney biopsy which demonstrates interstitial inflammation (mononuclear cell infiltrates), tubular injury, and tubulitis. Immunohistochemistry shows presence of virus in the tubular epithelial cells. SV 40 stains positively in the tubulointerstitium showing nuclear enlargement and smudged chromatin, suggesting viral inclusions as demonstrated in Fig. 11.3. Studies have suggested that BK nephropathy is due to an imbalance between BK virus replication and BK virus-targeted cellular immunity. Thus, the standard treatment for BK nephropathy is to reduce the immunosuppression with the aim of improving the T cell immunity against the virus [89, 90]. Antiviral agents such as cidofovir, brincidofovir, and leflunomide have also been used.

Case #5 Follow-up and Discussion:
The patient has adenovirus nephritis. Hematuria, flank pain, and acute kidney injury are the hallmarks of adenovirus nephritis clinically. The kidney biopsy confirmed viral inclusion bodies that are negative for SV 40 staining. In addition, the electron microscopy(not shown) revealed hexagonal-shaped viral particles, which confirmed adenovirus presence. The patient was treated with cidofivir but developed worsening renal failure due to cidofivir requiring renal replacement therapy. The Correct Answer Is a.

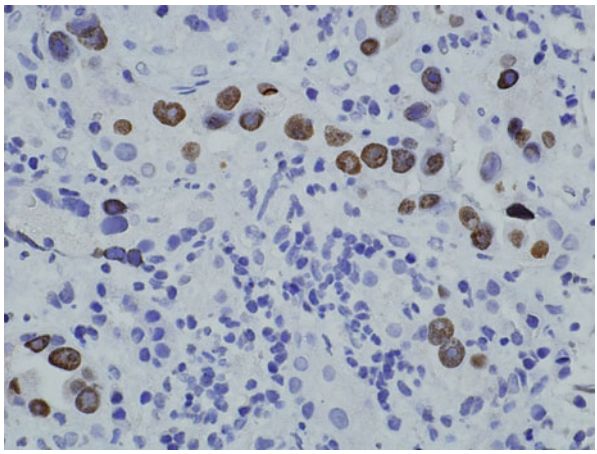

Fig. 11.3 SV 40 stain showing nuclear enlargement and smudged chromatin suggestive of viral inclusions in the tubular epithelial cells

Calcineurin Inhibitor Nephrotoxicity

Recipients of allogeneic transplants require calcineurin inhibitors for the prevention of GVHD. This is usually administered for the first 3 months following HSCT and tapered around day + 100. Patients who develop chronic GVHD require lifelong immunosuppression. Patients on long-term use develop chronic calcineurin inhibitor nephrotoxicity that is manifested by hypertension, tubular dysfunction, and glomerular/vascular disease. Kidney biopsy in these patients reveals obliterative arteriolopathy, ischemic collapse or scarring of the glomeruli, global and focal segmental glomerulosclerosis, focal areas of tubular atrophy, and interstitial fibrosis (striped fibrosis).

Idiopathic CKD

Patients who develop kidney disease after HSCT but do not fulfill the diagnostic criteria of NS, TMA, or viral infections are termed as having idiopathic CKD. It is speculated that this is caused by a combination of factors such as GVHD, along with the inflammatory state that accompanies it, as well as the medications, namely the calcineurin inhibitors used to treat it.

Management of HSCT-Related CKD

A thorough history is integral for the management of patients with CKD. One should review in detail the type of transplant (myeloablative versus non-myeloablative), conditioning regimen used (total body radiation/dose of radiation, type of chemotherapy), use of nephrotoxic medication, and history of AKI and SOS in the immediate

post-transplant period. Blood pressure should be checked at every visit. Skin should be examined to evaluate for the evidence of GVHD. Blood test should include complete blood cell count to evaluate the hemoglobin and platelets to assess for TMA. Renal function, namely blood urea nitrogen (BUN) and creatinine, should be tested at every visit. Routine urine microscopy should be done and proteinuria quantified. General treatment guidelines recommended for all patients with CKD are also applicable for patients who develop kidney disease in the post-HSCT period [91, 92]. In patients with evidence of TMA, it is imperative to control the blood pressure to reduce further endothelial damage. In rodent models of HSCT-related renal injury (radiation-induced HUS), the use of captopril or enalapril at the time of TBI resulted in less azotemia, lower blood pressure, decreased proteinuria, and long-term preservation of renal function [93]. In a study published by Cohen et al., use of captopril at the time of engraftment was associated with favorable trend towards a higher glomerular filtration rate (GFR; $P = 0.07$) and improved survival [94]. Since renin angiotensin system antagonists have shown to slow down progression of kidney disease and reduce proteinuria in renal diseases from various causes, they should be considered as first-line agents to treat hypertension in patients after HSCT. Hyperkalemia may be more common with their use and requires treatment with low potassium diet, diuretics, and sodium polystyrene [95]**.** Calcineurin inhibitor dose reduction may also become necessary sometimes, although alternatives may be limited in patients with GVHD. In addition, a kidney biopsy may be indicated prior to changes in immunosuppression to define the etiology of kidney disease. There is no evidence that plasma exchange is beneficial in TMA post HSCT, although it has been occasionally used in severe cases of TMA [96, 97].

Case #6
A 55-year-old male with history of non-Hodgkin's lymphoma undergoes a myeloablative allogeneic stem cell transplant. His post-transplant course is significant for the development of thrombotic microangiopathy associated with calcineurin inhibitors and acute kidney injury. His renal function continues to decline over the years despite lowering the calcineurin inhibitors, and hemodialysis is started 6 years post HSCT. Which of the following statements best describes his survival compared to a 55-year-old diabetic male on dialysis?
a. His survival on dialysis is the same as the 55-year-old diabetic male
b. His survival is better
c. His survival is worse

End-Stage Kidney Disease After HSCT

Patients who progress to end stage kidney disease (ESKD) and require dialysis after HSCT generally do poorly as compared to those who develop ESKD due to some other cause. In a single-center retrospective study of 1341 HSCT patients carried out

between 1985 and 2007, 19 patients (1.4 %) developed ESKD at a median of 7 years, which was 16 times higher than the expected age adjusted rate and far exceeded the relative risk of solid cancer developing post HSCT [98].

In a study published by Cohen et al. [99], patients who developed ESKD post HSCT had a significantly decreased survival as compared with non-BMT diabetic patients who were matched for age and start date of dialysis. Renal transplantation remains a good option. If a patient is to receive an allograft from the same donor as the original HSCT they will likely need minimal to no immunosuppression. Studies have shown that these patients have a good short-term survival and the primary cause of death is infection both in patients who received as well as those who did not receive immunosuppression [100, 101].

Case # 6 Follow-up and Discussion:
The patient will have a worse survival compared to a diabetic male matched for age and dialysis vintage. The Correct Answer Is c.

Summary

The presence of HSCT-related kidney complications leads to significant morbidity and mortality. The cause of renal dysfunction post transplant is multifactorial and is related to the conditioning regimen used during the transplant period, radiation, infections, and use of chemotherapeutic agents. The kidney injury is diverse and can affect the glomerulus manifesting as NS and TMA. Tubulointerstitial nephritis commonly is related to the drugs and infections. Since people with HSCT transplants live longer, prevalence of CKD is on the rise. Advances in our understanding of disease mechanisms will facilitate the prevention and treatment of these renal complications.

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Chapter 12
Radiation Nephropathy

Ilya G. Glezerman

List of Abbreviations

TBI	Total body irradiation
TMA	Thrombotic microangiopathy
MAHA	Microangiopathic hemolytic anemia
ESKD	End stage kidney disease
PRRT	Peptide-receptor radionuclide therapy
CKD	Chronic kidney disease
TCD	T-cell depleted
HSCT	Hematopoietic stem cell transplantation
PAI	Plasminogen activator inhibitor
RAS	Renin angiotensin system
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
TA-TMA	Transplant-associated thrombotic microangiopathy
CNI	Calcineurin inhibitor
HTN	Hypertension
GVHD	Graft versus host disease

Case #1
A 22-year-old female underwent matched unrelated T-cell depleted (TCD) hematopoietic stem cell transplantation (HSCT) for the treatment of acute myelogenous leukemia. Pre-transplant conditioning regimen consisted of fludarabine, thiotepa, and total body irradiation (TBI) with total dose of 13.75 Gy delivered in 11 fractions, three times a day. Baseline serum creatinine was 0.8 (0.6–1.3) mg/dL. Patient's post-transplant course was complicated by

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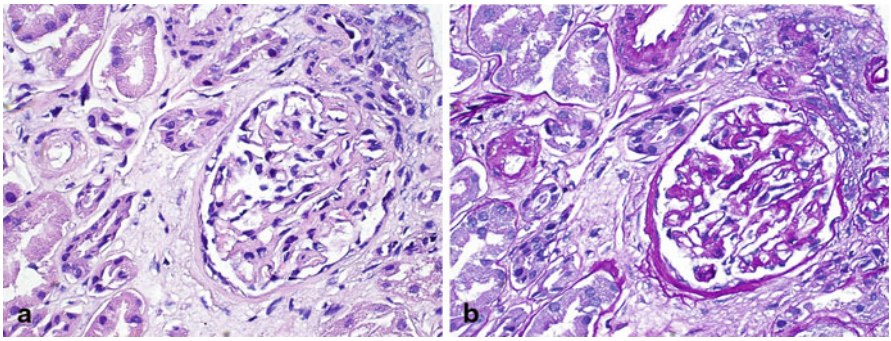

Fig. 12.1 Thrombotic microangiopathy. The figure showing changes of TMA (**a** hematoxylin and eosin stain, **b** periodic acid-Schiff stain) with peripheral capillary wall thickening and focal glomerular basement membrane duplication. *TMA* thrombotic microangiopathy. (Figure courtesy of Dr. Surya V. Seshan)

anthracycline-induced cardiotoxicity. Approximately 12 months after HSCT patient developed renal insufficiency with serum creatinine of 2.3 mg/dL. Urinalysis was mostly bland with only small blood. Random urine protein to creatinine ratio was 0.5. Serological as well as hemolysis work up was negative and the patient underwent kidney biopsy. She was started on an angiotensin converting enzyme inhibitor but her renal function continued to deteriorate and she required renal replacement therapy approximately 2 ½ years after HSCT. Figure 12.1a and 12.1b show the kidney biopsy findings.

What are the pathological features that one notices in the kidney biopsy consistent with radiation nephropathy? (choose all that apply)

a. Tubular injury with diffuse foot process effacement
b. Chronic interstitial damage
c. Thickening of glomerular capillary walls and double contours
d. Medial hypertrophy and intimal hyalinosis of arterioles and small arteries

Kidneys are dose limiting organ for radiation treatment of a number of oncologic conditions including gastrointestinal and gynecologic cancer, lymphomas, certain sarcomas as well as TBI in HSCT [1]. Radiation nephropathy as consequence of radiation exposure was first described in animal models close to 100 years ago and half a century later characterized in clinicopathological studies in humans by Luxton et al. as a syndrome consisting of hypertension (HTN), edema, anemia, and renal failure occurring 6–12 months after radiation exposure. Pathologic findings at the time showed an ill-defined hyaline obliteration of capillary loops, intertubular fibrosis and tubular atrophy, and various degrees of fibrinoid necrosis of arterioles and intralobular arteries [2].

Since the first description of radiation nephropathy, significant efforts were aimed at establishing kidney irradiation tolerance doses and kidney shielding. In addition,

more effective chemotherapy regimens were developed obviating the need for aggressive radiation. As a consequence, the incidence of radiation nephropathy has declined. However, more recently, radiation nephropathy reemerged in conjunction with the use of TBI in HSCT and it has been renamed in this setting as transplant-associated thrombotic microangiopathy (TA-TMA) [3, 4].

Pathophysiology

Most of the data regarding pathophysiology of early stages of radiation nephropathy are derived from animal studies as human data are only available in late-stage disease. Identification of target cells susceptible to radiation damage is somewhat difficult in the kidneys as there are a number of different cell types that vary in their ability to proliferate and regenerate after initial insult. Studies showed early damage to glomerular and juxtaglomerular cells with glomerular thrombosis indicating that glomerulus is an important target of radiation [5]. Electron microscopy of porcine model revealed that 3 weeks after 9.8 Gy single dose radiation exposure, there was glomerular endothelial disruption and leukocyte adherence followed by subendothelial expansion with electron-lucent material [6]. There is also activation of renal plasminogen activator inhibitor-1 (PAI-1) localized to the glomerulus. PAI-1-increase likely leads to impaired fibrinolysis and increased thrombosis as well as fibrosis via attenuation of plasmin-mediated matrix degradation. Mesangial cells are also involved in radiation nephropathy with mesangiolysis evident in murine models as well as human studies [6]. Vasculature was also noted to be affected by radiation. In canine model, the vascular damage occurs as early as 3 weeks after single 15 Gy dose exposure with arterioles and small arteries most affected. The changes are characterized by hyalinization of intima, endothelial swelling and/or proliferation, and hypertrophy and/or proliferation of smooth muscle. By 24 weeks the changes are more consistent with fibrinoid necrosis and fibrosis of the vessel walls. Authors also identified tubular damage in their model. By 9 weeks, there was significant parenchymal loss and tubular atrophy, however, a number of cells showed evidence of regeneration and by week 11 there was significant improvement in volume and function of tubular epithelium. However, between weeks 13 and 24 there was a second wave of tubular atrophy believed to be secondary to vascular damage [7].

The role of renin angiotensin system (RAS) in radiation nephropathy is suggested by a number of animal studies which showed mitigation of the severity of the disease with administration of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). However, there is no evidence of activation of RAS per se. In both pig and murine models blood renin levels were low or normal [8].

Prior exposure to certain chemotherapy agents can potentiate radiation damage to the kidney. In a rat model of TBI (17 Gy) followed by bone marrow transplant, the renal function decreased in the dose-dependent fashion in the animals exposed to cisplatin or carmustine 3 months prior to TBI [9]. Busulfan, high dose cyclophosphamide, and fludarabine have also been reported as risk factors for TA-TMA [4, 10].

The pathological findings on kidney biopsies done in patients with radiation nephropathy reveal evidence of TMA including vascular endothelial damage with endothelial cell dropout, subendothelial widening, and double contours of the glomerular basement membrane. There is also mesangiolysis, platelet aggregation in capillary loops, glomerular capillary thrombi, red cell fragmentation, thickening of glomerular arteriolar intimal layer as well as tubular atrophy [11, 12]. The precipitating event is believed to be endothelial damage leading to dysregulated interaction between platelets and glomerular endothelium resulting in microthrombi and ischemic end organ damage. Another hypothesis was proposed to explain multitarget nature of radiation injury. Glomerular radiation injury may lead to egress of pathologic mediators into urinary space and this leakage might produce parenchymal fibrosis if tubular denudation is present [6].

Dose Tolerance

The renal tolerance to radiation therapy is largely determined by the use of either whole field (bilateral kidney irradiation) or partial field (unilateral uniform or unilateral segmental kidney radiation). The whole field radiation patients are further divided into subgroup of patients receiving TBI.

In the whole field radiation (excluding TBI), total dose associated with 5 % probability of renal dysfunction after 5 year (TD 5/5) range from 14 Gy delivered in two fractions to 23 Gy delivered over 5 weeks. TD 50/5 (50 % probability of renal dysfunction after 5 year) was 28 Gy [13].

TBI radiation tolerance data are somewhat complicated by the fact that the patients in this group are generally sicker and exposed to a number of nephrotoxic therapeutic and chemotherapeutic agents. Multivariate analysis of 12 studies reporting on nephrotoxicity (elevated creatinine or development of TMA) in a mixed pediatric and adult patient population undergoing TBI showed that the dose associated with 5 % risk of renal dysfunction was 9.8 Gy regardless of fractionation schedule (median dose 12 Gy; range 75–14; median fractions 6, range 1–11, delivered once or twice daily) [1]. In addition to the radiation dose, prior exposure to fludarabine, cyclosporine, and teniposide has also been shown to increase the risk of renal dysfunction after TBI [1]. Partial kidney irradiation also carries the risk of renal dysfunction. It has been shown that doses of 26–30 Gy delivered unilaterally are likely to eliminate functions in the irradiated kidney [5]. Treatment of one kidney and its renal artery may produce renal artery narrowing leading to renal artery stenosis and high renin HTN. This side effect is more common in infants and children and should be distinguished from other causes of radiation associated HTN. Both vascular surgery approach and nephrectomy have been used to address this phenomenon [5].

Clinical Features

Radiation nephropathy is characterized by late onset and generally manifests 6–12 months after exposure to radiation. The clinical features include worsening renal function, edema, new or worsening HTN, and microangiopathic hemolytic anemia (MAHA). Renal dysfunction is generally gradual in onset and after a period of rising serum creatinine most patients enter a more stable state. However, some patients may progress to end stage kidney disease (ESKD) [4]. Evidence of hemolysis with anemia disproportionate to the degree of chronic kidney disease (CKD), thrombocytopenia, elevated serum lactate dehydrogenase levels, low serum haptoglobin, and schistocytes on peripheral smear may support the diagnosis of MAHA. However, not all patients develop MAHA. Some patients have kidney limited TMA with renal dysfunction, edema, and HTN as the only manifestations [14]. In patients with no evidence of MAHA the diagnosis of TA-TMA could be made clinically due to high degree of clinical suspicion or by renal biopsy. Recently, two working groups' guidelines and one validation study were published to address noninvasive diagnostic criteria for TA-TMA [4]. Unfortunately, all three guidelines rely on laboratory hematologic parameters of MAHA and are likely to miss patients with isolated renal TMA.

Most patients undergoing TBI in conjunction with HSCT also are treated with calcineurin inhibitors (CNI) to prevent or treat graft versus host disease (GVHD). CNI are well documented to cause both renal dysfunction and TMA [15]. Therefore it is often difficult to distinguish the causative agent of TMA. In a classic review, Pettitt and Clark proposed four distinct but overlapping subtypes of TA-TMA [16]. First is an early onset (20–100 days post HSCT) type which occurs in patients receiving CNI. The risk factors included GVHD, CMV infections, and intense pre-transplant conditioning. The course is rapidly progressing and commonly fatal. This type was termed fulminant, multifactorial TMA. In the second, late onset (> 6 months), type the manifestations are predominantly renal with HTN, edema, and renal failure in association with MAHA but with minimal systemic manifestations and absence of significant GVHD. TBI is noted as a predisposing factor particularly if unfractionated or given with multiple chemotherapeutic agents. This type was named conditioning associated TMA. The remaining two subtypes are strongly associated with CNI use and manifest as either nephrotoxicity or neurotoxicity of these agents with clinical improvements after CNI discontinuation.

Case #1 Follow-up and Discussion

The pathological findings on kidney biopsies done in patients with radiation nephropathy reveal evidence of TMA (choice C and D) including vascular endothelial damage with endothelial cell dropout, subendothelial widening, and double contours of the glomerular basement membrane. There is also mesangiolysis, platelet aggregation in capillary loops, glomerular capillary thrombi, red cell fragmentation, thickening of glomerular arteriolar intimal layer as well as tubular atrophy.

Treatment

The treatment for radiation nephropathy and TA-TMA is largely supportive with HTN control and treatment of complications associated with CKD. Because RAS was implicated in pathogenesis of radiation nephropathy in animal studies, the randomized trial of captopril to mitigate development of CKD after HSCT was conducted by Cohen et al. [17]. Authors enrolled 55 patients undergoing TBI and HSCT. Patients were randomized to captopril or placebo groups and both were started at engraftment and continued for 1 year. In 1-year survivors, the serum creatinine was lower ($p = 0.2$) and calculated GFR was higher ($p = 0.07$) in captopril group but neither was statistically significant. The incidence of TA-TMA was also lower in captopril group ($p = 0.1$) albeit also not statistically significant. Authors concluded that there is a trend in favor of captopril in mitigation of CKD after TBI and HSCT. However, only five patients in each group received 1 year of treatment and average length of captopril use was 1.8 months.

Plasmapheresis has been employed for treatment of TA-TMA, however, its response rate is $< 50\,\%$ with some case series showing virtually no response [18, 19]. Since radiation endothelial damage believed to be the initial event in pathogenesis of radiation nephropathy, lack of response to plasmapheresis in not surprising.

Case # 2

A 71-year-old male was referred to the tertiary cancer center for management of metastatic neuroendocrine tumor. At presentation serum creatinine was 1.5 mg/dL. Patient was receiving dihydropyridine calcium channel blocker and a non-selective β blocker for HTN. The renal ultrasound was unremarkable. Approximately 2 months after the initial diagnosis he underwent treatments with radiolabeled octreotide at an outside institution. He received 205 mCi dose of ^{90}Yttrium-DOTA-Tyr3-octreotide (^{90}Y-DOTATOC) followed by two treatments with 200 mCi of ^{177}Lutetium-DOTA-Tyr3-octreotide (^{177}L-DOTATOC) 2 and 4 months after ^{90}Y-DOTATOC. He was seen in renal clinic 9 weeks after the last dose of ^{177}Lu-DOTATOC for management of HTN. His blood pressure was 190/90 despite antihypertensive medications. His weight had increased by 6 kg with evidence of peripheral edema. The laboratory data showed serum creatinine of 2.0 mg/dL, Hgb of 9.9 (13–17) g/dL, platelet count of 84 (160–400) K/mcL, LDH of 324 (60–200) U/L. Peripheral blood smear was positive for occasional schistocytes. Haptoglobin level was 78 mg/dL (30–200). Urinalysis showed small albumin, moderate blood but only 1–2 RBC per high-power field and was otherwise bland. Random urinary protein to creatinine ratio was 1.2. Based on the clinical picture the diagnosis of radiation nephropathy was made. The kidney biopsy was not obtained. He was started on ARB and placed on a loop diuretic. The HTN and edema improved, however, the renal function continued to deteriorate and thrombocytopenia and anemia persisted. Five and

a half months after last treatment with ^{177}Lu-DOTATOC renal replacement therapy was initiated. He died due to progression of disease 1 month later.

When is the usual time frame of development of radiation nephropathy related with peptide receptor radionuclide therapy?

a. 6–12 months
b. 9–12 weeks
c. 13–24 months
d. 1–2 weeks

Peptide Receptor Radionuclide Therapy

Along with TBI, parenteral radioisotope therapy has led to recent reemergence of radiation nephropathy. Peptide-receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs has been effective in treatment of neuroendocrine tumors. Since somatostatin receptor is expressed on a surface of neuroendocrine tumor cells, octreotide (somatostatin analog) labeled with radionuclide can be delivered directly to the cancerous cells for therapeutic effect. In addition to octreotide analogs, radiolabeled gastrin, cholecystokinin, and exendin analogs are being investigated for treatment of tumors expressing their respective surface receptors [20].

Most radiolabeled peptides weigh less than 12 kDa and are filtered across glomerular basement membrane. In the proximal tubules, somatostatin analogs are reabsorbed via active receptor mediated endocytosis. Once taken up by the proximal cells the peptides are metabolized in the lysosomes to amino acids and radiolabeled catabolites. These catabolites may become trapped in lysosomes leading to relatively high retention of radioactivity in the kidneys [20]. Due to renal excretion of the peptide analogs, kidneys are the critical organ in patients treated with PRRT. In vivo studies showed that there is a wide inter-patient variability in the ^{90}Y-DOTATOC uptake in the kidneys, making it difficult to apply conventional dosimetry methods [21]. More complex models accounting for patient-specific kidney volumes and rates at which absorbed doses were delivered are required. Using these models dosed > 45 Gy correlated with rapid decline in renal function [22]. This dose is higher than in external beam radiation but the tissue reaction to the radiation does not depend only on absorbed dose. Other factors such as dose rate, fractionation, and distribution of the dose in the organ as well as type and energy of radiation may affect organ toxicity. Typically, PRRT has lower dose rates, less homogeneous distribution in the organ, and shorter range of radiation penetration as compared to external beam radiation [20].

Case # 2 Follow-up and Discussion
Advanced CKD and ESKD have been reported as a consequence of the treatment with PRRT [23–25]. The presentation is typical of radiation nephropathy with signs and symptoms developing 6–12 months after treatment. When kidney biopsy is performed, the findings were consistent with TMA. The answer is a.

Several strategies have been employed to alleviate renal toxicity of PRRT. Co-infusion of basic amino acids lysine and arginine has been shown to competitively inhibit proximal reabsorption of the radiolabeled peptides and currently is a standard reno-protective regimen in PRRT therapy. Use of ^{177}Lutetium instead of ^{90}Yttrium has also been associated with less renal toxicity likely due to lower β energy resulting in lower β emission and lower radiation dose to the glomeruli [20].

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Chapter 13
Dysproteinemias and Kidney Disease

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List of Abbreviations

C3NeF	C3 nephritic factor
CLL	Chronic lymphocytic leukemia
CR	Complete response
CSH	Crystal storing histiocytosis
DDD	Dense deposit disease
EM	Electron microscopy
ESKD	End stage kidney disease
GBM	Glomerular basement membrane
FLC	Free light chains
HCDD	Heavy-chain deposition disease
IF	Immunofluorescence
ITG	Immunotactoid glomerulonephritis
LCDD	Light-chain deposition disease
LCFS	Light chain Fanconi syndrome
LHCDD	Light–heavy chain deposition disease
LPL	Lymphoplasmacytic lymphoma
MBL	Monoclonal B-cell lymphocytosis
MCN	Myeloma cast nephropathy
MIDD	Monoclonal immunoglobulin deposition disease
MG	Monoclonal gammopathy
MGRS	Monoclonal gammopathy of renal significance

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MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MPGN	Membranoproliferative glomerulonephritis
NSAIDS	Nonsteroidal anti-inflammatory drugs
OS	Overall survival
PGNMID	Proliferative glomerulonephritis with monoclonal IgG deposits
PLEX	Plasmapheresis
SAP	Serum amyloid P
SLL	Small lymphocytic lymphoma
SMM	Smoldering multiple myeloma
TBM	Tubular basement membrane
THP	Tamm–Horsfall protein
WM	Waldenstrom's macroglobulinemia

Dysproteinemia is the condition in which a monoclonal gammopathy (MG) is produced as the result of proliferation of a clone of B-cell origin, often a plasma cell. MG can occur in benign or malignant hematologic conditions. The benign form is known as monoclonal gammopathy of undetermined significance (MGUS). In this condition, the serum monoclonal (M) spike is < 3 g/dl and there should be no more than 10 % plasma cells in the bone marrow [1]. As the name implies, no end organ damage can be attributed to the MG. MGUS can be the result of a clonal proliferative disorder such as monoclonal plasmacytosis, monoclonal B-cell lymphocytosis (MBL) or low-grade B-cell lymphomas. By definition, MGUS is benign but can transform to a more sinister hematologic disorder, most often to multiple myeloma (MM). In general, the risk of transformation is approximately 1 % per year indefinitely [2]. This risk does not decrease with time. The premalignant and malignant conditions include smoldering multiple myeloma (SMM) and MM, lymphoma such as lymphoplasmacytic lymphoma (LPL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). LPL is the hematologic disorder associated with Waldenström's macroglobulinemia (WM). These conditions are characterized by their higher proliferative rates and organ damages.

Kidney injury is a common finding with dysproteinemia [3]. There are two common misconceptions regarding kidney diseases of dysproteinemia. First, the development of kidney disease requires a malignant condition. Studies have shown that human renal lesions can be duplicated in animals using only monoclonal proteins isolated from the urine of patients with dysproteinemia-associated kidney diseases [4]. This is also observed clinically in which the majority of patients with immunoglobulin light chain (AL) amyloidosis and approximately one third of patients with monoclonal immunoglobulin deposition disease (MIDD) do not have MM or other malignant conditions [5, 6]. To better illustrate this point, the term monoclonal gammopathy of renal significance (MGRS) is now used to describe premalignant hematologic conditions with MG that result in kidney disease [7]. Second, certain kidney diseases arise from specific clonal disorder. In reality, while preferences do exist, the kidney disease is ultimately determined by the monoclonal protein and not the cell that makes it. For example, cast nephropathy is most often the result of MM, but it has been described in CLL and LPL. Similarly, 65 % of cases of

immunotactoid glomerulonephritis also have CLL but it has been reported in MM and LPL [8].

Monoclonal proteins can injure the kidney in a number of different ways. There are several methods of categorizing the different paraprotein-associated kidney diseases. One is by the compartment where the injury takes place. For example, fanconi proximal tubulopathy and cast nephropathy are mainly confined to the tubular and tubulointerstitial compartment, while MIDD and AL amyloidosis are more likely to involve the glomerular compartment. However, there are overlaps as AL amyloidosis may involve the glomerular, tubular, and vascular compartments. Another method of categorization is by the pathogenic mechanism that engenders kidney injury. This is the method that will be used in this chapter. Amyloidosis is described in detail in the following chapter and will not be discussed further in this chapter.

Deposition (Non-organized)

Case #1
A 58-year-old female presents with an elevated creatinine for 3 years. This was first noted during her hysterectomy. Since then, her creatinine has been slowly increasing until it reached 2.4 mg/dl. Initial urinalysis showed only microscopic hematuria. Urologic evaluation with ultrasound and retrograde pyelogram was unremarkable. She had a blood pressure of 162/95 mm Hg and a pulse of 92. Heart examination revealed an S4. Lungs were clear to auscultation bilaterally. Edema was 3+ bilaterally. Proteinuria was measured at 2.8 g/d. Urinary albumin was 72 % and a small monoclonal IgG kappa was identified. No M-spike was identified on serum protein electrophoresis but a monoclonal IgG kappa was detected on immunofixation. Serum kappa free light chain was 447 mg/dl and lambda was 0.673, with a ratio of 664.

What is the most likely pathology on the kidney biopsy?

a. Light chain cast nephropathy
b. MIDD
c. AL amyloidosis
d. Membranous nephropathy

Monoclonal Immunoglobulin Deposition Disease

The best example a deposition disease with non-organized MG deposits is MIDD. MIDD is actually a group of diseases characterized by the non-fibrillar deposits of monoclonal protein in soft tissue. They include light-chain deposition disease

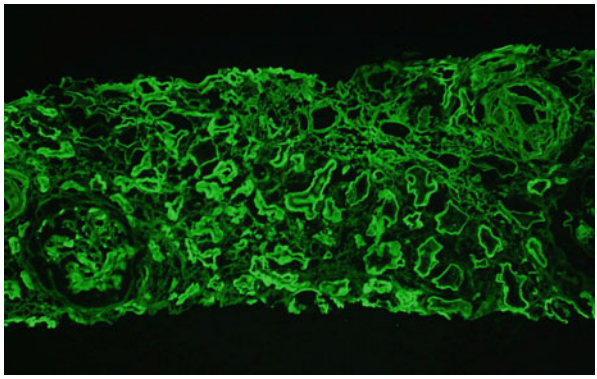

Fig. 13.1 Immunofluorescence microscopy with antisera to kappa light chain shows prominent staining of tubular basement membranes (TBM) in a linear pattern. Staining can also be seen in the glomerulus along some GBM as well as the mesangium in a nodular pattern

(LCDD), light–heavy chain deposition disease (LHCDD), and heavy-chain deposition disease (HCDD) [9]. It was first recognized in the 1950s when diabetic glomerulosclerosis-like lesions were described in patients with MM without diabetes [10]. The first MIDD described was LCDD in an abstract by Antonovych in 1974 and later by Randall in a manuscript in 1976 [11]. Unlike amyloid and immunotactoid, these deposits are amorphous to granular. The most common MIDD is LCDD and the rarest is the HCDD. MIDD can be seen in 5 % of MM patients in autopsy series [12]. This is approximately half the incidence of AL amyloidosis. In addition to the kidney, MIDD has also been reported in lungs, heart, liver, and even brain [13, 14]. Kidney manifestations however is the predominate presentation [6, 9].

Clinical Case #1 Follow-up and Discussion

A kidney biopsy performed showed nodular sclerosis of the mesangial regions by periodic acid–Schiff (PAS)-pale and silver-negative material with associated mild mesangial hypercellularity. Red blood cell casts were identified. There was 3+ linear staining along tubular and glomerular basement membranes (GBM) for kappa light chain with negative staining for lambda light chain. Staining of the mesangial regions by kappa light chain (3+) was also noted (Fig. 13.1). Numerous punctate powdery mesangial and capillary loop (intramembranous and subendothelial) electron-dense deposits were noted on electron microscopy (EM). Bone marrow biopsy showed 40 % kappa light chain-restricted plasma cells. Bone survey was positive for small lytic lesions in the humeri and femora. The diagnosis of MIDD with MM was made. Patient was treated with cyclophosphamide, bortezomib, and dexamethasone for four cycles followed by autologous stem cell transplantation. A complete hematologic response was achieved. One year after the stem cell transplantation, her creatinine was 1.6 mg/dl and proteinuria was 149 mg/dl.

Renal impairment and proteinuria are seen in almost all patients with MIDD. The median age of presentation is between 51 and 57 years but ranges from 22 to 94 [6, 9, 15, 16]. Roughly two thirds of the patients were male. Median proteinuria ranges between 2.7and 4.1 g/d from different series [6, 9]. Nephrotic syndrome can be seen in 40 % of the patients. One series found that patients with HCDD may have higher degree of proteinuria. Microscopic hematuria is common (62 %) but gross hematuria is rare (3 %). Renal insufficiency is also nearly universal with an average serum creatinine of 3.8 mg/dl at presentation. During follow-up, 39–57 % of patients had reached end stage kidney disease (ESKD). Median overall survival (OS) varied from 13 months in one study to 90 months in another [9, 16]. Renal histology, presence of MM, and presence of lytic bone lesion were among the factors that influenced survival.

Histologically, the most recognizable lesion of MIDD is the nodular mesangial sclerosis [9, 11, 17, 18]. This is present in two third of the cases [9, 11, 17, 18]. These nodules are positive on PAS stain and Jones' silver stain and indistinguishable from to Kimmelstiel–Wilson nodules, although some feel there is less variation in size as compared with diabetic nephropathy. Other features include mesangial sclerosis without nodules, membranoproliferative pattern, and even crescents. The diagnosis is made on immunofluorescence (IF) where the monoclonal light chains, heavy chains, or entire immunoglobulin (Ig) can be seen staining in linear pattern diffusely along GBM and tubular basement membranes (TBM). Deposits can also be seen in the mesangium, but it is less reliable than the TBM or GBM. In the vessel walls, the monoclonal protein is deposited in a web-like pattern. Deposits of C3 may also be found in patients with LCHDD and HCDD. The diagnosis is confirmed on EM. The deposits should be electron dense and appear powdery or amorphous in the same compartments as in IF. MIDD often can coexist with other renal lesion in the same kidney. Cases of coexistence with myeloma cast nephropathy (MCN), AL amyloidosis, and fibrillary glomerulonephritis have been reported [19, 20].

One area of controversy is in the diagnostic criteria for MIDD. Some have suggested that both IF and EM deposits are needed for the diagnosis, while others feel that only IF deposits are necessary. In one single center series of 64 patients, every patient had deposits identified on IF and EM [9]. On the other hand, an Italian series of 63 patients found IF was positive in 97 % of cases while EM was only positive in 77 % [6]. This has also been noted in a smaller series where the IF was positive in 95 % of the 40 patients while granular deposits were found in only 73 % of the biopsies [21]. The EM negative cases often had MCN within the same biopsy [6, 22]. It is important to recognize that the sensitivity of the technique depends on the location in the kidney. Deposits nearly are universally found (> 95 %) in the TBM using IF but are more likely to be found in the GBM rather than TBM when using EM (74–47.8 % vs 56–34.8 %, respectively) [9, 21]. Data for the renal outcomes of patients with IF only deposits are not available; however, the coexistence of cast nephropathy does alter the renal and patient outcomes [16].

In older series, a monoclonal protein was not always found in patients with MIDD. For example, monoclonal protein by immunofixation was only identified in the serum in 76 % of the patients, urine in 90 % of the patients, and neither in 6 % of the patients

in the Pozzi study [6]. In the Nasr study, 100 % of the patients who had serum-free light chain assay performed had an abnormal result [9]. Serum-free light chain assay is particularly useful in patients with HCDD in which the immunoglobulin heavy chain is often truncated [23]. In these patients, the truncated heavy chains are sometimes difficult to detect by immunofixation technique. However, all these patients have abnormal free light chain and free light chain ratio [9]. On bone marrow biopsy, MM was diagnosed in 59–65 % of cases while 3 % were due to CLL [6, 9]. The rest which were described as idiopathic, would now be classified as MGRS [7].

Monoclonal kappa light chains are much more common than their lambda counterparts in LCDD. Approximately 75 % of the reported cases are from a kappa clones [6, 9, 18, 24]; and within the kappa subtypes, V_{kI} seems to be most common [25]. The reason why kappa light chains are overrepresented may be due to its tertiary and quaternary structure. Analyses of kappa light chains show a β-edge in the CDR2 loop resulting from a conserved cis-proline at position 8 [26]. This proline is in the trans-position in lambda light chains. Not only that, in the lambda light chains, it is often followed by another trans-proline at position 9. Exposure of the β-edge promotes spontaneous aggregation of kappa light chains into oligomers that elongate into a fibril. These fibrils do not bind serum amyloid P (SAP) or Congo red-like amyloid fibrils so they do not have amyloid characteristics. These oligomers may form the deposits that are seen in MIDD.

Prognosis both from renal survival and patient survival are quite variable in MIDD and are dependent on several factors. Coexistence with MM or MCN adversely affects both renal and patient survival [16]. Patients who present with both MIDD and MCN rarely 9.1 % recover their renal function versus 43.5 % of those presenting with MIDD alone. Median OS for patients with MIDD is 48 months versus 21 months for those with MIDD and MCN ($p = 0.0453$). In another study where only 21.0 % of the patients had MM found the patient survival at 5 years was 71 % but the renal survival was 40 % [15]. Inadequate treatment of the MGRS was felt to be the reason for the high rate of ESKD. Obviously, access to effective chemotherapy plays a large role in both renal and patient survival. In a modern series of 64 patients where 20 % had symptomatic MM and access to novel agents for myeloma therapy, the median OS was 90 months [9].

Treatment of MIDD should be based on the clone responsible for the monoclonal protein [27]. In patients with MM or CLL, appropriate treatment of the underlying hematologic malignancy should be used. In patients with MGRS (≤ 10 % bone marrow plasma cells), treatment with cytotoxic therapy is indicated in order to preserve renal function [16]. However, because these patients do not have a malignant condition, minimizing chemotherapy-related toxicity is as important as efficacy. Bortezomib-based therapies have become a popular choice in the treatment of MIDD because of their lack of nephrotoxicity and renal metabolism [28, 29]. It does have some serious long-term side effects such as peripheral neuropathy that requires every effort to reduce as much toxicity as possible especially in patients with only MGRS [30]. Autologous stem cell transplantation either alone or after induction has also

produced good results [19, 29,31–33]. Finally, it is important to note that ESKD patients without MM who are not candidates for kidney transplantation may not require therapy [7, 27].

Kidney transplantation in MIDD may be possible if the clone can be suppressed. Studies have found recurrence to be as high as 80 % in the patients who still have a monoclonal protein [34]. Thus, kidney transplantation should be reserved for those patients who had a hematologic complete response (CR). This is defined as the absence of the monoclonal protein in the serum and urine, absence of clonal plasma cells in the marrow, and normal serum-free light chain ratio. The last criterion is sometimes difficult to assess as the ratio changes with advanced chronic kidney disease [35]. Kidney transplantation is often more difficult in patients with MM since their disease tends to relapse more often than those with MGRS [19].

Membranoproliferative Glomerulonephritis with Monoclonal Deposits

Case #2
A previously healthy 35-year-old female presented with sudden onset of hypertension, microscopic hematuria, and 10 g/d of proteinuria. Creatinine was 0.8 mg/dl. Initial kidney biopsy was read as LHCDD. Serum and urine protein electrophoresis were negative. A bone marrow biopsy was performed which was inadequate for interpretation. Patient was initially started on cyclophosphamide and prednisone. Thalidomide was later added but was discontinued due to side effects. Creatinine increased to 1.4 mg/dl and proteinuria was 8.8 g/d. Proteinuria responded (1.4 g/d) but due to the development of acalculous cholecystitis, cyclophosphamide was stopped. Creatinine increased to 1.9 mg/dl. Patient was started on mycophenolate mofetil but proteinuria began to increase. A course of rituximab was administered without any benefit. Proteinuria increased to 4.5 g/d and cyclophosphamide and prednisone was restarted. Proteinuria stabilized but creatinine began to climb. Tacrolimus was started but both proteinuria and creatinine increased. After 5 years of initial presentation, dialysis was initiated for end-stage kidney disease. After 3 years on dialysis, patient received a kidney transplant. At the time of transplantation, a monoclonal IgA lambda was identified in the blood and urine. After 3 months of posttransplant, the creatinine was 1.4 mg/dl and proteinuria was 1.7 g/d. Serum kappa free light chain was 12.3 mg/dl and lambda was 8.65 mg/dl, with a ratio of 1.43. An allograft biopsy showed membranoproliferative glomerulonephritis (MPGN) with deposits that stain for IgA and lambda but not kappa. The deposits have a crystalline structure with a periodicity of 20 nm. By 4 months

posttransplant, creatinine increased to 3.3 mg/dl. If the IF showed no C4D deposition in the above case, what secondary causes have to be considered for the MPGN pattern of injury?

a. Lymphoma
b. Myeloma
c. Hepatitis B or C
d. CLL

Another example of non-organized MG deposition disease is MPGN. Until recently, MG was thought not to be associated with MPGN. However, a new classification scheme based on pathophysiology rather than histology recognized MG as a major contributor to MPGN. In the new classification, MPGN is divided into those with immunoglobulin (Ig) deposits and those with only complement components [36]. The ones with complement deposits only are due to activation of the complement cascade usually due to dysregulation. The ones with Ig deposits are further divided between those with polyclonal Ig deposits which are usually secondary to infections or autoimmune disorders and those with monoclonal Ig [36, 37]. This new classification is supported by a single center study from the Mayo Clinic which found 41 % of the cases were associated with a circulating monoclonal protein and monoclonal Ig deposits in the kidney after excluding cases with hepatitis (B and C) and dense deposit disease (DDD) [38]. While majority of the cases were classified as MGRS, 21 % met criteria for MM. Other hematologic diagnosis included WM, CLL, and other lymphomas.

The injury pattern is that of membranoproliferative pattern. The glomeruli are enlarged with expansion of mesangium and hypercellularity [38]. GBM are thickened often with eosinophilic deposits and double contours as a result of new membrane formation. Cellular elements include mononuclear cells as well and neutrophils. Crescents are not uncommonly seen in many biopsies. Focal global glomerulosclerosis, tubular dropouts, and interstitial fibrosis can be found in more advanced cases. On IF, the monoclonal Ig deposits are most commonly found along the capillary walls. C3 may also be seen in the same areas as the monoclonal Ig. Deposits can also be found in the mesangium but less often than capillary walls. The Ig deposits should be restricted to a single immunoglobulin light chain and immunoglobulin heavy chain subclass. On EM, the electron-dense deposits do not have substructures and are often granular in appearance. They are mainly subendothelial on the capillary walls. Deposits can also be found in the mesangium.

Clinical Case #2 Follow-up and Discussion
A bone marrow biopsy showed 30 % lambda light chain-restricted plasma cells confirming the diagnosis of MM. Patient began treatment with cyclophosphamide, bortezomib, and dexamethasone.

Similar to native kidney MPGN pattern of injury, secondary causes such as viruses and malignancies have to be ruled out. Prognosis of patients depends on the presence of MM. In one series, 50 % of the patients had died within 2 years of follow-up and only one patient had stable chronic kidney disease [38]. Of the 16 patients with MGRS, 6 had stable renal function, 2 had declining renal function, 2 progressed to ESKD, and no data were available for 6 patients. After kidney transplantation, 75 % of the patients with MPGN and monoclonal Ig deposits had a recurrence in the renal allograft [39]. All of the recurrences were detected within 12 months of kidney transplantation.

Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID)

PGNMID represents another kidney disease characterized by non-organized deposits [40, 41]. As the name suggests, PGNMID usually present with a proliferative glomerulonephritis. This is often in a diffuse endocapillary proliferative glomerulonephritis pattern. This feature is characterized with endocapillary hypercellularity often with leukocyte infiltration and luminal occlusion. PGNMID often overlaps with MPGN pattern and can present with crescents and membranous pattern. On IF, granular staining of monoclonal Ig can be detected often along with C3 deposits. On EM, deposits are confined to the glomerular compartment. They are most often deposited in the subendothelial compartment of the capillary wall but subepithelial and intramembranous deposits can also be found less frequently. In some cases, a crystalline lattice substructure can be identified. An IgA variant has also been described [42].

Whether PGNMID represents a subset of MPGM with monoclonal deposits or is a separate entity is still debated. PGNMID does have some unique features. First, it has a preference for monoclonal IgG3. Approximately two third of cases are IgG3 with IgG kappa making up 50 % of the reported cases. Another characteristic is the low rate of MM. In a series of 37 patients, only 1 patient had symptomatic MM. In fact, less than 30 % of the patients had a detectable circulating monoclonal protein at the time of diagnosis. Despite that, both MPGN associated with a monoclonal protein and PGNMID recur with high frequency after kidney transplantation [39, 43].

Renal prognosis for these patients is poor. During a median follow-up of 30 months, 37.5 % of patients had persistent chronic kidney disease and 21.9 % progressed to ESKD [41]. Death occurred in 15.6 %, two of whom died of metastatic carcinoma. Treatment was received by 56.3 % and only 10 % received cytotoxic or anti-myeloma therapy. Recurrence is high after kidney transplantation. In one series of four patients, recurrence was detected on average 3.8 months after kidney transplantation [43]. Aggressive treatment with rituximab and/or cyclophosphamide resulted in improvement of the proteinuria in these patients; however, graft lost is not uncommon after recurrence. Early detection and initiation of effective therapy may be the difference in some cases.

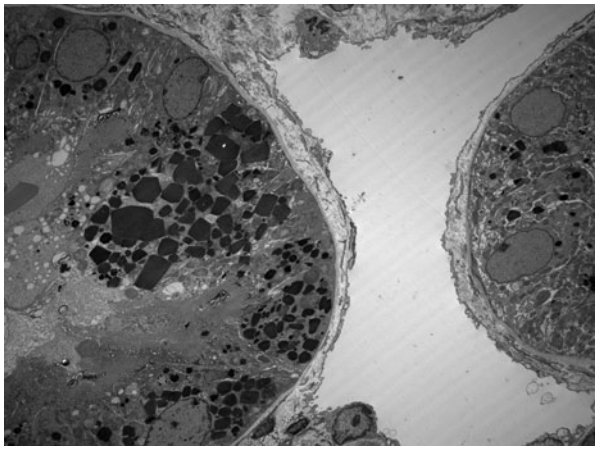

Fig. 13.2 EM showing multiple electron-dense intracellular crystalline structures in the proximal tubules

Case #3

A 75-year-old female presented for evaluation of chronic kidney disease. Patient had a one and a half year history of malaise. She was taking substantial amounts of nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of degenerative joint disease, primarily of the hands. She developed a cold and began taking decongestant and antihistamine medications. This impaired her driving and ability to write legibly which led her to seek medical attention. Her creatinine was noted to be 3.6 mg/dl up from her baseline of 1.9 mg/dl. Proteinuria was measured at 2 g/d. A kidney biopsy was performed which showed an active tubulointerstitial nephritis. She was treated with 8 weeks of high-dose tapering prednisone. Her symptoms improved but her creatinine remained in the low 3s. Additional testing found an IgG kappa in the serum with an M-spike of 1 g/dl and kappa free light chain of 26.4 mg/dl, lambda of 2.38 mg/dl, and a ratio of 11.1. A bone marrow showed 5–10 % plasma cells. Her kidney biopsy was reviewed and in addition to the tubulointerstitial nephritis, numerous intracytoplasmic crystalline inclusions within tubular epithelial cells, associated with preferential tubular epithelial cell staining for kappa versus lambda light chain (Fig. 13.2). Pertinent laboratory findings include a uric acid level of 2.4 mg/dl, phosphorus of 4.1 mg/dl, glycosuria, and elevated urine cysteine and glycine levels. What is the most likely diagnosis?

a. MIDD
b. Light chain Fanconi syndrome
c. AL amyloidosis
d. Cast nephropathy

Deposition (with Organized Deposits)

Light Chain Fanconi Syndrome and Proximal Tubulopathy

Light chain Fanconi syndrome (LCFS) is a rare condition characterized by crystalline deposition of monoclonal light chains in the proximal tubules. The Fanconi syndrome (FS) refers to the electrolytes wasting that occurs. Other crystalline deposition diseases include cryocrystalglobulinemia and crystal storing histiocytosis (CSH). In CSH, the crystals are found in the cytoplasm of histiocytes in the bone marrow and other organs. Like CSH, nearly 90 % of the clones in LCFS are kappa restricted with V_{kI} seem to be the most common [44, 45]. Nearly half of the patients will have a diagnosis MM. Other diagnoses include WM, CLL, smoldering MM, and MGRS.

Clinical Case #3 Follow-up and Discussion
Patient was treated with six cycles of bortezomib and dexamethasone. Kappa free light chain was reduced to 11.4 mg/dl with a ratio of 5.28 corresponding to a partial response. However, creatinine increased to 4.2 mg/dl. Because of this cyclophosphamide was added and treatment continued for another 15 cycles. Kappa free light chain was reduced to 3.80 mg/dl with a ratio of 4.71, and creatinine decreased to 2.1 mg/dl. Proteinuria was unchanged at 588 mg/d. The above case demonstrates a case of LCFS.

The median age of patients with LCFS is 57 years with 58 % male patients. Commonly, these patients present with non-nephrotic range proteinuria and renal insufficiency. In addition, patients often present with glycosuria, bone pain, osteomalacia, nontraumatic fractures, and fatigue. Electrolyte abnormalities including hypouricemia (66 %), hypophosphatemia (50 %), and hypokalemia (44 %) are common [44]. It is important to recognize that the electrolyte abnormalities become less significant as renal function declines. However, aminoaciduria should always be present followed by normoglycemic glycosuria (100 %). Phosphaturia is present in less than half of the patients (43 %). Renal tubular acidosis may be present. In cases where glycosuria or phosphaturia is absent, an incomplete FS is diagnosed. Rarely, distal tubular dysfunction including distal renal tubular acidosis and nephrogenic diabetes insipidus can occur along with the proximal tubular dysfunction [46–48]. The mechanism for this is not well understood but it is possible that other renal disease processes may be involved [46].

The most common feature seen on kidney biopsy for LCFS is patchy tubular injury. Intracytoplasmic microcrystals can be seen in flattened or enlarged proximal tubular cells [45, 49]. Crystals can be confirmed with toluidine-blue stain. On IF, the crystals should stain for a single light chain. IF on pronase-digested, paraffin-embedded tissue is more sensitive than standard IF on frozen tissue for demonstrating

kappa light chain in the crystals [50]. Crystals are often rhomboid in shape and are seen in the cytoplasm inside lysosomes on EM [51]. Varying degree of tubular atrophy and interstitial fibrosis may be present. Rarely coexistent cast nephropathy can be identified within the same biopsy [52].

The renal outcome in LCFS is variable. In one series, 5 out of 32 patients reached ESKD while 8 out of 11 did in another series [44, 45]. Interestingly, MM does not appear to be a risk factor for progression to ESKD [44]. It is unclear whether ESKD can be prevented by effective therapy since most of the reports came from melphalan and prednisone era. In fact, treatment with alkylator was a risk factor for death as these patients died of treatment related infections. A recent report described improvement or stabilization of renal function after treatment with bortezomib-based therapy in two patients [53]. Both had a significant decrease in their serum kappa FLC levels.

The term light chain proximal tubulopathy is often used with LCFS but consensus is lacking. Some use the term to refer to crystalline deposition with partial FS while others use it to describe proximal tubular injury without crystals [49, 54]. Some feel they are the same disease while others feel they are separate entities [55, 56]. In one series, 3.2 % of the biopsies associated with a paraprotein-related disease were identified as light chain proximal tubulopathy [54]. The definition used was presence of deposits restricted to a single immunoglobulin light chain in the cytoplasm of the proximal tubule. Only 3 out of 13 patients had crystalline deposits and 10 had monoclonal lambda light chain deposits. Of the patients with crystals, 2 had monoclonal kappa light chain deposits. Proteinuria and progressive renal insufficiency with proteinuria were the primary indications for renal biopsy in patients without crystals. Lysosomal or mitochondrial abnormalities along with signs of acute tubular injury such as cytoplasmic swelling or blebbing and flattening or dilatation of tubules and loss of brush border were demonstrated in all patients. Out of 13 patients, 8 were diagnosed with MM. In contrast, only 1 out of 190 biopsies of patients with MM was diagnosed with light chain proximal tubulopathy in another single center study [57]. Clearly, more research is needed to better define light chain proximal tubulopathy.

Immunotactoid Glomerulonephritis

Case #4

A 70-year-old male with a history of psoriatic arthritis presents with 5-month history of progressive renal insufficiency and proteinuria. On routine medical examination, the patient was discovered to have a Scr of 1.63 mg/dl. Baseline creatinine 1 year ago was 1.32 mg/dl. Two months later, it had increased to 2.14 mg/dl. Blood pressure had also become more labile amlodipine and nebivolol were started. Patient had been on celecoxib for approximately 2

years and he took ibuprofen on rare occasions. His other medication includes adalimumab which was recently switched from etanercept. He denies any rashes, fever, chills, or night sweats. He does have some numbness in his right arm which is associated with his neck pain. He had two previous episodes of nephrolithiasis which required lithotripsy. Outside urinalysis shows (3+) proteinuria and (3+) hematuria. Twenty-four hour urine showed 9.1 g/d of proteinuria. Serum and urine protein electrophoresis were negative for monoclonal proteins.

His blood pressure was 167/94 with a pulse of 68. Heart and lung exam were normal and he had no lower extremity edema. A renal biopsy was performed which showed mesangial and endocapillary proliferative features and focal segmental scarring. IF studies demonstrate reactivity for IgG, C3, and kappa with minimal to negative staining for lambda light chain. IgG subtyping demonstrates predominant staining with IgG1 (2+) and IgG2 (trace) and is negative for IgG3 and IgG4. Ultrastructural studies demonstrate subepithelial and mesangial electron-dense deposits organized in microtubular substructures (Fig. 13.3). A diagnosis of immunotactoid glomerulonephritis (ITG) is made.

What is the range of diameter of the fibrils found in ITG?

a. 7–10 nm
b. 12–30 nm
c. > 30 nm

ITG is a rare glomerular disease characterized by organized Ig deposition in the glomerulus [58]. The fibrils in ITG are usually much larger than amyloid fibrils and fibrils from fibrillary glomerulonephritis and they do not stain with Congo red. Their mean diameter is 31 nm with a range of 17–52 nm [8]. Amyloidosis fibrils are classically randomly arranged in 7–10 nm and fibrillary GN would have randomly arranged fibrils in the 12–30 nm range. Some have reported fibrils as thin as 9 nm [59]. The one feature that distinguishes ITG from amyloid and fibrillary fibrils is their hollow center which is similar to microtubules [8]. ITG, however, is indistinguishable from cryoglobulins, and by definition cryoglobulinemia must be ruled out. Unlike the fibrils in amyloidosis and fibrillary glomerulonephritis, the microtubules in ITG are usually arranged in parallel arrays [59]. Other differences in the fibrils can be detected using proteomics by mass spectrometry. A small study found the microtubules of ITG have a different ratio of immunoglobulin to SAP component and apolipoprotein E than those of AL amyloid, fibrillary, and cryoglobulin [60]. When fibrillary glomerulonephritis and ITG were first discovered, some had felt that they were two spectrum of the same disease, but evidence based on fibril characteristics and association with hematologic malignancy really support two distinct and separate entities.

Histologically, over half of the cases of ITG show a membranoproliferative patterns on light microscopy [8]. Mesangial expansion and global double contouring are often seen. The next most common pattern is membranous either segmental or global

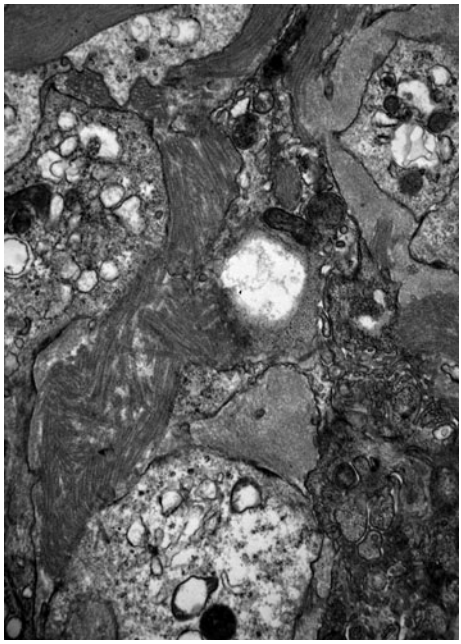

Fig. 13.3 EM of mesangium and subepithelial deposits. These deposits are organized in *parallel arrays* and have a diameter of 35–40 nm. On cross-section, these fibrils have a *hollow center* which is characteristic of microtubule

characterized by thickened membranes and spike formation. The least common pattern is endocapillary proliferation with hypercellularity and leukocyte infiltration resulting in luminal obstruction. Eosinophilic hyaline pseudothrombi and crescents are sometimes seen in the glomerulus [59]. IF is usually positive for the entire immunoglobulin, and in contrast to fibrillary glomerulonephritis, shows light chain restriction [57, 59, 61].

Proteinuria is heavy with ITG with a median of 11.1 g/d (range 1.4–36 g/d) [57, 59, 61]. Microscopic hematuria is common. Median Scr at presentation is 1.5 mg/dl (0.7–3.8 mg/dl). Median age of these patients ranges from 59 to 66 years. There is male predominance ranging from 71.4 to 83.0 %. ITG is often associated with an MG. In reported series, it is involved with an MG in 63–86 % of cases which in contrast to fibrillary glomerulonephritis is only involved in 15–17 % of cases. The most common hematologic diagnosis associated with ITG is CLL. In some series, it is up to 50 % of cases. However, it can be associated with MM and was found in 12.5 % of cases in another series [8].

The rarity of ITG makes it difficult to conduct any clinical trials. Treatments successful in reducing the lymphocyte clones also succeeded in maintaining renal function and reducing proteinuria [59]. Treatment with steroids combined with alkylating agents such as cyclophosphamide and melphalan have been successfully used. Chlorambucil-based therapy seems particularly effective at achieving partial and complete remission. Rituximab was reported to have stabilized the proteinuria and renal function in a case of recurrent ITG in a renal allograft [62]. Rituximab followed

by alemtuzumab successfully reversed the proteinuria completely in a patient with CLL and ITG [63].

Clinical Case #4 Follow-up and Discussion
The diameters in ITG are usually in > 30-nm range. Correct answer is c. Adalimumab was discontinued without any benefit to his renal function. Creatinine rose to 4.0 mg/dl. Cyclophosphamide and prednisone were started and creatinine improved to 2.3 mg/dl. Proteinuria improved to 3.9 g/d. Unfortunately, patient developed profound diarrhea and anemia requiring hospitalization. Cyclophosphamide was discontinued. Creatinine slowly increased after discontinuation of cyclophosphamide despite 30 mg of prednisone daily. Patient began to develop steroid myopathy. The decision was made to switch therapy to rituximab. While waiting for insurance approval, creatinine began to rise. Intravenous cyclophosphamide was administered without any benefits. Creatinine rose to 4.3 g/d. Rituximab was finally approved and administered. Creatinine fell to 2.8 mg/dl and proteinuria was reduced to 0.7 g/d. Five months later, creatinine again rose to 3.7 mg/dl. Proteinuria was stable. Rituximab was administered again. Creatinine has been stable for the past 6 months.

Cryoglobulinemia

Cryoglobulins are immunoglobulins that reversibly precipitate in cold temperatures. The precipitation results in vasculitic symptoms including rash, ulcers, ischemia, arthralgia, neuropathy, fatigue, renal disease, etc. [64]. Cryoglobulins are categorized into three types. Type I cryoglobulins are the composed of monoclonal Igs usually IgM and IgG. Type II cryoglobulinemia is characterized by the both monoclonal IgM and polyclonal IgG which is the rheumatoid factor activity that is unique to type II cryoglobulinemia. Only polyclonal Igs usually IgG is in type III cryoglobulinemia. Type II and III can be the result of chronic infections particularly hepatitis C and autoimmune diseases such as Sjorgren's syndrome.

Approximately 30 % of cryoglobulinemia involve the kidney [64, 65]. Clinically, patients present with proteinuria, hematuria, renal insufficiency, hypertension, and other signs of vasculitis. Histologically, cryoglobulinemia often present in a membranoproliferative pattern. Glomerular cellular proliferation, segmental necrotizing lesions, and hyaline thrombi in the glomerular capillaries are common features. Vasculitic features are sometime present in arterioles and small-sized vessels. In type I and II cryoglobulinemia, hyaline thrombi should show light chain restriction. Cryoglobulins on EM have a characteristic appearance of paired, curved microtubular structures that are between 20and 30 nm in diameter. Deposits can be found in

the epimembranous, subendothelial, and mesangial region of the glomerulus. Unfortunately, these features are not specific and are reminiscence of those of ITG. Distinction must be based on biologic characteristics of the Ig.

Type I and II cryoglobulins contain monoclonal Ig. Type I cryoglobulinemia is often the result of LPL causing WM, but other low grade non-Hodgkin lymphomas such as marginal zone lymphoma, follicular lymphoma, mantle cell lymphoma can also produce cryoglobulins [64, 66, 67]. CLL and IgM myeloma are rare causes of cryoglobulinemia. A small case series found type I cryoglobulinemia is much more common in men but there is no predilection for kappa versus lambda light chain [66]. Type II can be the result of a clonal disorder or infections. The most common infection causing cryoglobulinemia in the world is hepatitis C. In these patients, antiviral therapy should be tried first. Rituximab can be used along with antiviral therapy and can be quite effective. In patients with clonal disease, treatment should be directed toward the clone responsible for producing the cryoglobulin [27]. Treatment using standard myeloma therapy has been successful [66, 68]. This would include corticosteroids, alkylating agents, and novel agents such as thalidomide, lenalidomide, and bortezomib [66, 67]. Treatment of cryoglobulinemia as a result of a lymphoma should include corticosteroids and rituximab. Purine analog and chlorambucil may be used in cases involving CLL. Renal response with steroids alone is approximately 60 % while response to rituximab as frontline agent is 85 %. Multivariate analysis found rituximab plus steroids were more effective than steroids alone in achievement of a CR but alkylating agents plus steroids were only more effective at achieving a lower steroid dose [67]. Rituximab plus steroids were associated with more severe infections as compared to corticosteroids alone. Alkylating agents plus steroids resulted in the least severe infections but no differences were noted in the death rates among the three regimens. Cryoglobulinemia can recur after kidney transplantation [64]. Treatment should be the same as native kidney disease.

Tubular Obstruction

Light Chain Cast Nephropathy

Case #5
A healthy 70-year-old female with history of controlled hypertension and urinary tract infections presented with chest pain with soreness and tightness in her anterior neck when walking. Initially, the chest pain was thought to be heartburn, but it became more frequent and began occurring at rest. After a month, she was referred to a cardiologist who performed an angiogram. This showed an 80 % proximal LAD lesion. She underwent angioplasty and

stenting. The procedure was apparently uncomplicated. Preoperatively her creatinine was 1.0 mg/dl and BUN 17 mg/dl. Post-procedure creatinine and BUN were unchanged, but 2 weeks later, creatinine was 9.0 mg/dl and BUN was 59 mg/dl. She was seen by a Nephrologist who performed a kidney biopsy. This showed morphologically normal glomeruli without mesangial hypercellularity or sclerosis. Tubules are dilated and contain hard waxy/hyaline casts with fractures, clinging tubular epithelium, and giant cell reaction. Focally, TBM are disrupted and there are inflammatory cells destroying tubules. Most inflammatory cells are plasma cells. Hemoglobin was 10.8 g/dl and calcium was 9.8 mg/dl. Serum protein electrophoresis did not detect an M-spike but immunofixation was positive for a monoclonal kappa. Serum kappa FLC was 618 mg/dl and lambda FLC was 3.34 mg/dl, with a ratio of 185.03.

What are the most important factor(s) associated with the recovery of renal function?

a. The percentage of pathologic free light chain reduction.
b. The percentage of reduction in the M-spike.
c. The time to free light chain reduction.
d. A and C
e. A, B and C

Light chain cast nephropathy (CN) is the most common cause of kidney impairment in MM patients. Cast nephropathy is identified in 32–48 % of patients who died with a diagnosis of MM [12, 69, 70]. In a study of MM patients with severe renal impairment, CN was present in 86.6 % of the patients who had renal histology evaluated [71]. Although it is commonly referred to as myeloma kidney or MCN, CN can also occur in patients with WM and CLL [72, 73]. In the setting of a plasma cell proliferative disorder, CN is a myeloma defining event as it is a consequence of high tumor burden [74]. One study found only 3 % of patients with renal impairment were classified as having low tumor load [75]. In CN, the serum FLC level is more important than the M-spike [76, 77]. MCN is also more common in light chain only MM and biopsy proven MCN is extremely rare in patients with less 70 mg/dl of serum FLC [77, 78]. In fact, majority of the patients with CN have a serum FLC above 100 mg/dl [79].

Urine FLC excretion is another important aspect in the pathogenesis. The median proteinuria is 2.0 g/d in patients with MCN but albumin makes up only 7 % of the total protein [80]. Most of the protein in urine is Bence-Jones protein. One study found elevated levels of urine FLC levels in 98 % of the patients with renal impairment [81]. This makes sense since the pathogenesis of CN is due to tubular obstruction by light chain casts [82]. Normally, excess FLCs are produced in the manufacturing of immunoglobulins. The excess FLCs are freely filtered by the glomerulus and reabsorbed in the proximal tubule via a receptor-mediated endocytosis [83]. After uptake by the megalin and cubilin receptor, the FLCs are transported intracellularly where

they undergo degradation inside a lysosome. In some patients with MM, WM, and CLL, the monoclonal FLCs markedly overproduced. This overcomes the proximal tubule's ability to reabsorb all of the FLCs allowing them to enter the loop of Henle in high concentrations where they come in contact with Tamm–Horsfall protein (THP). Some FLCs have an affinity toward THP and will bind and coaggregate when they come into contact with THP. The binding site on the FLCs has been located on the CDR3 region which is attracted to the carbohydrate moiety of THP [84]. This explains why some patients can excrete large amount of Bence-Jones protein without ever developing CN [85, 86]. Additionally, the obstructed tubules induce an intense inflammatory response probably through urine leak of FLC into the interstitium [87]. Experiments have shown that monoclonal free light chains are capable of producing hydrogen peroxide. Hydrogen peroxide generated by monoclonal FLC can activate the NFκB pathway to induce monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6) [88].

Aside serum FLC levels, several external factors can contribute to the development of CN. The most important of which is dehydration or prerenal state [89]. Prerenal state decrease urine flow rate and increases the urinary concentration of LC. The concentration of urinary THP, sodium chloride, calcium, pH, and furosemide can also influence the binding and aggregation. Medication may also play a role. Nonsteroidal anti-inflammatory drugs are well known to cause cast nephropathy [71]. In one study, 23.5 % of the patients with renal failure were attributed to NSAID use. Other nephrotoxic drugs have also been implicated. Intravenous contrast has also been associated with renal failure in myeloma patient. It is estimated that the incidence is eightfold higher in myeloma patients than controls [90]. While this sounds high, the rate peaks at 1.25 % suggesting that it is still safe for MM patients to receive intravenous contrast studies if medically necessary.

Histologically, MCN is characterized by the presence of intratubular light chain casts in the distal tubules and collecting ducts [78]. On IF, casts usually stain brightly for a single immunoglobin light chain. The casts often have a fractured appearance due to the crystalline structure which can be seen on EM. Mononuclear cells form giant cells around casts in an attempt to remove them. Tubular injury is commonly seen in the biopsy. Interstitial inflammation may vary from minimal to intense interstitial nephritis and is likely dependent on the severity and duration of obstruction. In more chronic cases, chronic interstitial nephritis is common. It is important to note that MCN can also be found along with other renal lesions in the same kidney such as MIDD and AL amyloidosis [91].

AKI is the most common presentation for MCN and it is usually nonoliguric. Even in patients with severe renal failure (Scr > 11.0), only 50 % were oliguric [71]. Dehydration is the most common cause of MCN. In a study of patients with severe AKI (Scr > 11.0 mg/dl) due to MCN, dehydration was the number one risk factor present in 65 % of the patients [71]. It was triggered by hypercalcemia in 38.2 % of cases and infection in 26.5 %. NSAIDs were the cause in 26.5 %. This is unfortunate since patients are commonly prescribed or take NSAIDs over the counter for bone pain from compression fractures. Other nephrotoxic drugs include intravenous contrast which 23.5 % received prior to the development of AKI.

MCN usually present rapidly with AKI that develops over days [78]. These patients should have high levels of serum FLC and low urinary albumin excretion. Patient may present with AKI alone or in combination with other MM lesions. Prompt treatment is required. This includes elimination of the precipitating agent, correction of hypercalcemia and dehydration, and increased urine flow. Definitive treatment, however, needs to focus on the rapid reduction of serum FLC levels by chemotherapy and extracorporal removal. Two separate studies have found that a minimum reduction of serum FLC by 50 % is required for renal recovery [79, 92]. The speed at which this is accomplished is also important as the rate of renal recovery rate drops as the time to FLC reduction increases [77]. Renal recovery decreases drastically if FLC reduction cannot be achieved within 21 days.

Clinical Case #5 Follow-up and Discussion
The correct answer is d. Treatment with high dose dexamethasone was started along with PLEX. Patient never regained kidney function and was maintained on chronic hemodialysis. She underwent an autologous stem cell transplantation and achieved a very good partial response. Her disease relapsed 20 months later and she was started on bortezomib and dexamethasone which again had a very good partial response. Treatment however was complicated by disseminated zoster requiring intravenous acyclovir. She had a fall 8 months later, resulting in a subdural hematoma, and died 2 months later as a result of complications. The use of plasma exchange along with chemotherapy is discussed below.

Effective chemotherapy is the key to the sustain reduction of serum FLC levels. It is beyond the scope of this chapter to discuss all of the chemotherapy available for MM. In principle, the choice of chemotherapy depends on whether the myeloma is newly diagnosed or relapsed. In chemotherapy naïve patients, agents that have high and rapid activity and are not renally cleared or metabolized are preferred [93]. They include bortezomib and thalidomide. Recently, pomalidomide and carfilzomib had been approved for use in relapse MM. Neither undergoes significant renal metabolism or clearance but experience in renal failure patients is still small. High-dose steroids may have added benefits in MCN due to its anti-inflammatory effects and ability to inhibit the production of hydrogen peroxide by the monoclonal light chains [94].

The benefit of extracorporeal light chain removal is controversial. The use of PLEX has been explored by three randomized trials and the results are mixed. Two of the trials including the largest one were negative; however, serum FLC was not used as a marker of response in any of the trials and renal biopsy was not used to confirm the diagnosis in the largest study [95–97]. A report found high rate of renal recovery (86 %) when PLEX was combined with a bortezomib-based therapy but others have found nearly as high rates of recovery with bortezomib-based therapy alone [94, 98]. Another large trial MyEloma Renal Impairment Trial (MERIT) is currently being conducted in the UK and is about to be completed and will hopefully shed more light on the subject. High cutoff (HCO) dialyzers with molecular cutoffs as

high as 45 kd have been used to remove FLC [99]. Kinetic studies have shown higher rates of FLC removal compared to PLEX. Promising results were demonstrated in a pilot study in patients who were able to complete the HCO dialyzers treatment [79]. Two randomized trials are currently being conducted with HCO dialyzers in MCN. Others have tried to bypass the requirement of hematologic response in developing compounds that directly act on the kidney. Two compounds have shown promising results in animal studies. Pituitary adenylate cyclase-activating polypeptide (PACAP38) is a 38-amino acid peptide which in addition to other activities has significant immunomodulatory effects [100]. In vitro studies have shown that it is capable of attenuating tubular cell injury resulting from exposure to monoclonal FLC. The second is a cyclized peptide constructed from the CD3 binding region of FLCs with high affinity toward THP. This cyclized peptide was designed to competitively block the binding of monoclonal FLC to THP [82]. Coadministration of the cyclized peptide with FLC capable of producing CN completely prevented the development in AKI in animals. Similar benefits have been demonstrated by delaying administration for up to 4 h after infusion of the FLC.

Complement Activation

C3 Glomerulonephritis

C3 glomerulonephritis is a recently described entity where the predominate deposit in the kidney C3. In these patients, C1q, C4, and Igs are not found in the biopsy. Majority of the case of C3 glomerulonephritis result from complement dysregulation. C3 glomerulonephritis is similar to DDD, but while the deposits in DDD are intramembranous, deposits in C3 glomerulonephritis can be located in the subepithelial, subendothelial, and intramembranous space. The deposits tend not to be as dense as those of DDD [101]. The complement dysregulation is often the result of a genetic mutation in one of the complement regulatory peptides. The most common mutation occurs in the factor H genes. Other mutations include complement factor H-related (CFHR) 5 genes, factor I, and CD46 [102]. Autoantibodies to factor H have also been implicated.

A C3 nephritic factor (C3NeF) has been identified in both patients with DDD and less commonly C3 glomerulonephritis. C3Nefs are factors that stabilize C3 convertase, which keeps the C3 activated via the alternative pathway. IgG autoantibodies have been identified as C3NeF initially by the Toronto group in 1977 and later verified by others in London and Paris [103–105]. It is interesting to note that in the original series of 17 patients, 3 of the patients' sera C3NeF activity was abolished by removal of IgG kappa using anti-κ light chain sepharose. The activity was maintained when anti-λ light chain Sepharose was used suggesting these antibodies may be monoclonal [103]. In a recent study of 41 patients with C3 glomerulonephritis, 10 had a monoclonal protein (6—IgGκ, 2—IgGλ, 1—IgA, and 1—IgMλ) [106]. Bone marrow biopsy in five showed plasma cells dyscrasia (< 10 % plasma cells) and one patient had 30 % involvement of a CLL. Two of these patients had C3NeF. In another series of six patients from France, four had monoclonal IgGκ and IgGλ [107].

Although none had a C3NeF, only three had detectable genetic mutations of the complement regulation pathway and one had an IgG autoantibody to factor H. Patients from both studies who received cytotoxic therapy (including corticosteroids with alkylating agents, bortezomib and CLL therapy with rituximab, cyclophosphamide, vincristine, and prednisone) had reduction on proteinuria and maintenance of kidney function while two of the four patients treated with just angiotensin converting enzyme blockade had progression to ESKD.

Summary

As laboratory testing for monoclonal protein improves, so has our understanding of the relationship between monoclonal gammopathies and renal diseases. As we saw, a number of mechanisms have been identified for kidney injury from dysproteinemia, including protein deposition, and protein-mediated tubular obstruction and complement activation. From MGUS to myeloma, all spectrums of plasma cell dyscrasias have been associated with renal disease. Confirming the association of kidney disease with MG is essential, and treatment is geared toward elimination of the clone.

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Chapter 14
The Amyloidoses

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List of Abbreviations

Apo-A1	Apolipoprotein A1
CKD	Chronic kidney disease
dFLC	Free light chain difference
ESKD	End stage kidney disease
FLC	Free light chains
FMF	Familial Mediterranean fever
HSCT	Hematopoietic stem cell transplantation
IF	Immunofluorescence
Ig	Immunoglobulin
IHC	Immunohistochemistry
ITT	Intention to treat
LCDD	Light-chain deposition disease
LCM-MS	Laser capture microdissection and mass spectrometry

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LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PAS	Periodic acid-Schiff
SSA	Serum amyloid A
TRM	Treatment-related mortality
TTR	Transthyretin

Brief History of Amyloid

The first documented clinical description of amyloidosis dates back to the 1600s. Thomas Bartholin, a Danish physician credited with the discovery of the lymphatic system, reported an autopsy case in which the spleen was so fibrous that it could barely be cut with a knife [1, 2]. This may be one of the first reports of the "sago spleen" of amyloidosis. The term amyloid was coined nearly 200 years later in 1838 by Matthias Schleiden, a German botanist, when describing a normal waxy component of plants [2]. In 1854, Rudolf Virchow was the first to apply the term to human tissue samples. He noticed both the paleness of the involved organs and the clinical association with edema. He was also the first to demonstrate the presence of amyloid in glomerular tissue and in the afferent arteries of the kidney. Virchow was frustrated at the infiltrative nature of amyloid and the inability to examine it as a distinct entity from the involved organs. He stated that "only when we have discovered the means of isolating the amyloid substance, shall we be able to come to any definite conclusion with regard to its nature [2]."

In 1922, Hans Herman Bennhold noted the relative specificity of Congo red, an aniline dye, for amyloid [3]. Five years later, two Belgians, a biochemist, Marcel Florkin, and a physician, Paul Divry, reported that amyloid appeared apple green when stained with Congo red and viewed under polarized light [4]. By the mid 1950s, Alan Cohen and Evan Calkins described the primary and secondary fibrillary structure of amyloid protein using electron microscopy [5]. The modern nomenclature and diagnosis will be examined below.

Amyloid Nomenclature and Diagnosis

The amyloidoses are a heterogeneous group of diseases that are unified by the characteristic deposition of a pathologic proteinaceous substance deposited in the extracellular space in various tissues of the body [6]. Under light microscopy and hematoxylin and eosin (H&E) stains, amyloid appears as an amorphous, eosinophilic, extracellular substance. By electron microscopy, amyloid is seen to be made up of continuous, nonbranching fibrils with a diameter of approximately 8–10 nm. This structure self-assembles to yield twisted fibers and is often called a cross β-pleated sheet because the β strands are orientated perpendicular to the fiber axis [7]. This

structure is identical in all types of amyloidosis. Through both its progressive accumulation and direct cytotoxicity to adjacent cells it contributes to organ dysfunction [8]. To differentiate amyloid from other hyaline deposits (e.g., collagen and fibrin), a variety of histochemical techniques can be used, the most common of which is the Congo red stain. For this stain, ordinary light reveals a salmon pink color of the tissue deposits, but under polarized light an apple-green birefringence pattern appears and is diagnostic of amyloid. To clarify this point, only the β-pleated fibril structure allows for the intercalation of the Congo red molecule to create the birefringence.

According to the 2010 Nomenclature Committee of the International Society of Amyloidosis, at least 27 different proteins have been recognized as causative agents of amyloid diseases [9]. Despite having heterogeneous origins and structures, all these proteins can generate morphologically indistinguishable amyloid fibrils. A system of amyloid fibril nomenclature based on the chemical identity of the amyloid fibril forming protein has been recommended. To be designated as an amyloid fibril protein, the protein must occur in tissue deposits and exhibit affinity for Congo red and display green birefringence when viewed by polarized light. Also, the protein must have been definitively characterized by protein sequence analysis (or DNA sequencing in the case of familial diseases). The nomenclature is based on the chemical nature of the fibril protein, which is designated protein "A" and followed by a suffix that is an abbreviated form of the precursor protein name. For example, when amyloid fibrils are derived from immunoglobulin light chains, the amyloid fibril is light chain amyloidosis (AL) and the disease is named AL amyloidosis (Table 14.1). Although a large number of intracellular protein inclusion diseases have been reported, such as the neurofibrillary tangles of Alzheimer's disease, with characteristics identical to the amyloid diseases (fibrils that stain positive with Congo red and emit apple-green birefringence), they are referred to as "intracellular amyloid" and are not discussed in this chapter. It is also important to determine the chemical identity of an amyloid fibril protein in a patient with systemic amyloidosis because amyloid proteins are synthesized by different organs. The protein origin may dictate different therapeutic approaches, such as a liver transplantation or hematopoietic stem cell transplantation [10]. For example, the familial amyloidoses are chemically and clinically heterogeneous and are also associated with antiquated nomenclature, such as "familial amyloid polyneuropathy." It is important to use the modern nomenclature, (e.g., ATTRV30M or ATTRY78F which represent the familial form of mutated transthyretin (TTR)-induced amyloid) to avoid confusion with the more frequently occurring AL amyloid, for which the treatment plan would be markedly different. Serum amyloid A (SAA), TTR, and immunoglobulin kappa (Ig-κ), or lambda light chains (Ig-λ; primary AL amyloid) constitute 90 % of all systemic amyloidosis.

It is now known that some amyloid fibrils may serve biological function(s). These protease-resistant β-pleated sheet assemblies are widely used in nature and comprise the so-called functional amyloids. In fact, amyloid formation seems to be an intrinsic propensity of polypeptides in general and the amyloid β-pleated sheet is a highly conserved structure through evolution. Functional amyloids have been found in a wide range of organisms, from bacteria to mammals, with functions as diverse as biofilm formation, development of aerial structures, scaffolding, regulation of melanin

Table 14.1 Common amyloid syndromes and their precursor proteins

Amyloid type	Protein	Abbreviation	Organ involvement	Comment
Immunoglobulin light chain	Monoclonal Ig light chain	AL	Kidney, liver, heart, GI tract, peripheral and autonomic nerves, soft tissues	Acquired plasma cell dyscrasia with synthesis of protein from bone marrow
Fibrinogen	Fibrinogen Aα	AFibα	Kidney, liver, spleen	Hereditary; hypertension common
Reactive	SAA	AA	Kidney, GI tract, liver, autonomic nervous system	Secondary to chronic inflammation, infection or neoplasm; protein synthesized from liver
Senile systemic	TTR wild type	ATTR-wt	Cardiac	Usually older males; protein synthesized from liver
TTR	TTR mutant	ATTR	Peripheral and autonomic nerves, heart, eye, occasional kidney	Hereditary; protein synthesized from liver
Apolipoprotein AI	Apolipoprotein AI	AApoI	Kidney (glomerular), liver heart, skin, larynx	Hereditary
Apolipoprotein AII	Apolipoprotein AII	AApoII	Kidney	Hereditary
Dialysis related	β2-microglobulin	Aβ 2M	Osteoarticular tissue, GI tract, blood vessels, heart	Inadequate renal clearance of protein
Lysozyme	Lysozyme	ALys	Kidney, liver, GI tract, spleen, lymph nodes, lung, thyroid, salivary glands	Hereditary

SAA serum amyloid A, *TTR* transthyretin, *GI* gastrointestinal, *Ig* immunoglobulin, *AA* serum amyloid A protein amyloidosis

synthesis, epigenetic control of polyamines, and information transfer [11]. Presently, one of the methods under development for the treatment of amyloid disease involves directly inhibiting the formation of pathological amyloid. Given that pathological and functional amyloid share a common structure, some amyloidogenesis inhibitor drugs intended to prevent disease could disrupt functional amyloid formation. This could lead to undesirable side effects because functional amyloid seems to have a role in vital physiological processes in humans, including hemostasis and melanin

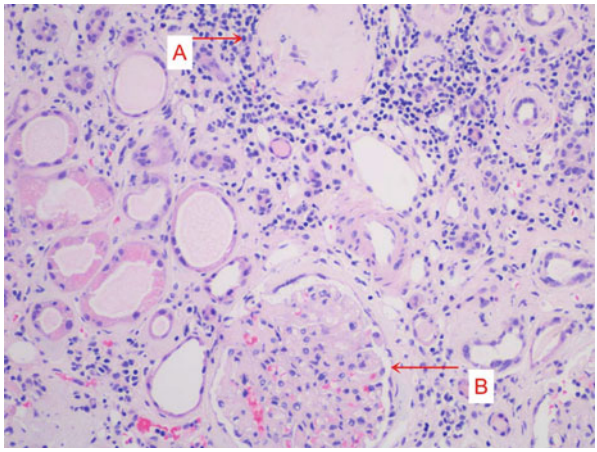

Fig. 14.1 Section shows obliteration of the glomerulus by amyloid deposition, (**a**). Glomerulus with slight thickening of the capillary membranes and mild expansion of the mesangium by amyloid deposition, (**b**). H&E, 200X

synthesis [7]. Thus, amyloidogenesis inhibitor drugs must be designed with sufficient specificity to avoid interfering with these functions.

Case #1
Mr. P is a 69-year-old man with an 8-year history of type II diabetes who was followed by a nephrologist for renal insufficiency with a creatinine clearance of 45 ml/min and proteinuria of 5.3 g/day. His diabetes was well controlled with oral medications and he never required insulin. In addition, he had no evidence of diabetic retinopathy. For this reason, his nephrologist suspected that there was likely another etiology of his renal insufficiency and proteinuria and he was referred for a kidney biopsy. On H&E staining, Mr. P's kidney biopsy demonstrated mild amorphous, eosinophilic deposition in the glomerulus, mesangium, and capillary membranes (see Fig. 14.1). A completely hyalinized glomerulus stained pink-red with Congo red (See Fig. 14.2). The same area showed apple-green birefringence with polarization (see Fig. 14.3).

What is the most likely diagnosis after the above biopsy result findings?

a. AL Amyloidosis
b. AA Amyloidosis
c. Minimal change disease
d. Diabetic nephropathy
e. More information is required.

The kidney is most frequently affected in AL, AA, and several of the hereditary amyloidoses. Kidney biopsy is often required to identify the underlying disease. Amyloid deposits can be seen throughout the kidney but predominate in the glomerulus [12]. By light microscopy, amyloid appears as an amorphous, eosinophilic material in the mesangium and capillary loops. When amyloid is suspected, the tissue for Congo red

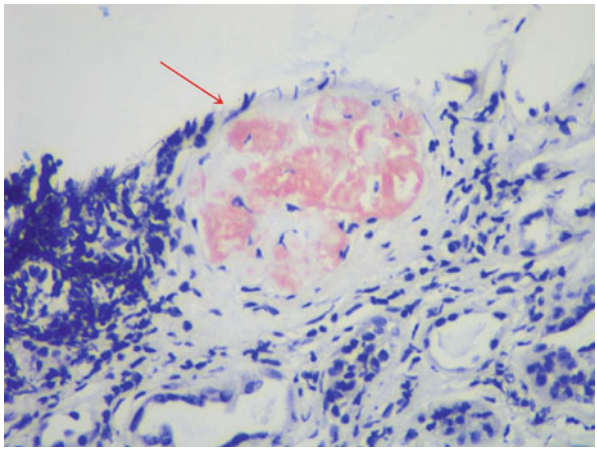

Fig. 14.2 Congo red stained section shows pink-red amyloid in the glomerulus (*arrow*). Congo red, 400X

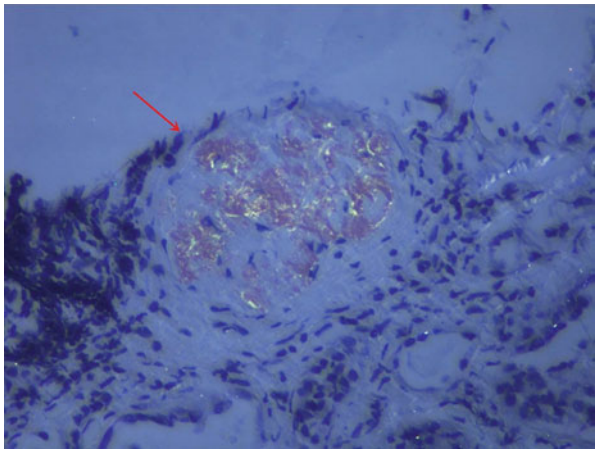

Fig. 14.3 Yellow-green birefringence with polarization (*arrow*). Congo red, 400X

staining should be cut at 10-micron thickness, rather than the 2-micron sections that are normally prepared from renal biopsies. Amyloid deposition in the tubulointerstitium can also lead to tubular atrophy and interstitial fibrosis even in the absence of significant glomerular deposition. Regardless of the location of the amyloid deposits, birefringent Congo red staining is seen. Because the amyloid fibrils are composed primarily of the amyloid protein and not extracellular matrix polysaccharides such as collagen, periodic acid-Schiff (PAS) staining is only weakly positive. Glomerular deposition often leads to significant proteinuria in the nephrotic range with rates up to 20 g/day. Since the protein is primary albumin, the associated edema can be severe and refractory to diuretics, as well as difficult to manage, especially in the setting of cardiac dysfunction and autonomic neuropathy seen in some amyloid subtypes. Conversely, when glomerular involvement is minimal and amyloid deposition is primarily in the tubulointerstitium, the resulting proteinuria is minimal, glomerular filtration is reduced, and creatinine is increased. Immunofluorescence (IF) and

immunohistochemistry (IHC) are negative for intact immunoglobulin, complement and fibrin, but in AL amyloid are frequently positive for immunoglobulin light chain.

Although amyloid fibril deposition is often evident on kidney biopsy by electron microscopy, it can be overlooked if the index of suspicion is not sufficiently high. The fibrils are nonbranching, randomly arrayed, and have a diameter of 8–10 nm. The diagnosis of amyloid may be missed if there is secondary effacement of epithelial foot processes affected by amyloid deposition in the setting of only mild amyloid deposition in the mesangium. Such pathologic findings can give the false impression of minimal change glomerulonephritis [13]. Misdiagnosis may also occur due to confusion with the morphologic appearance of diabetic nephropathy. In a study of 26 cases of both AA and AL renal amyloidosis, there were many morphologic changes seen that mimic diabetic nephropathy; such as diffuse and nodular patterns, capsular drop-like deposits along Bowman's capsule, deposition in the afferent and efferent arterioles, early stage glomerular microaneurysm, and accumulation of amyloid along the tubular basement membrane [14].

Case #1 Follow-up and Discussion

The correct answer is e. Congo red staining can define presence of amyloidosis but the type of amyloidosis is still very important to determine for treatment purposes. As stated above, IF and IHC are negative for intact immunoglobulin, complement, and fibrin in AA amyloidosis, but in AL amyloid are frequently positive for immunoglobulin light chain. For confirmation of diagnosis, Mr. P's biopsy specimen was also sent to the Mayo Clinic for laser capture microdissection and mass spectrometry (LCM-MS)-based proteomic analysis and was determined to be AL λ-type amyloidosis.

Serum amyloid P component is a normal plasma protein that constitutes approximately 5 % of all amyloid deposits. It is a member of the pentraxin family of proteins that are involved in the acute inflammatory process, another example of such is C-reactive protein. Of note, radiolabeled serum amyloid P component scintigraphy is a noninvasive and quantitative method for imaging amyloid deposits, which produces diagnostic images in most patients with systemic amyloidosis, and can be used repeatedly to monitor the course of the disease. However, it has not been produced commercially and has very limited availability [15].

Renal disease is common in many forms of amyloid and a major source of morbidity. Without treatment, end stage kidney disease (ESKD) will usually occur at variable rates over time. However, some forms of amyloid such as senile systemic (TTR protein) and dialysis-related amyloid (β2-microglobulin) do not typically involve the kidney.

The most common form of systemic amyloidosis is AL amyloidosis, with a reported incidence of 8.9 per million person years [10]. AL amyloidosis is of interest to the hematologist because it is caused by a neoplastic plasma cell or B-cell clone which synthesizes abnormal amounts of a specific immunoglobulin (Ig) which

results in the dysfunction of one or more involved organs. Systemic amyloid may also be seen in 5–15 % of individuals with multiple myeloma. AL amyloidosis should be suspected in any patient with nondiabetic nephrotic syndrome, nonischemic cardiomyopathy with an echocardiogram showing concentric hypertrophy, increase of NTproBNP in the absence of primary heart disease, presence of hepatomegaly or increase of alkaline phosphatase without an imaging abnormality, peripheral and/or autonomic neuropathy, unexplained facial or neck purpura or macroglossia. Any patient who presents with any one of these signs should undergo a biopsy to detect amyloid deposits and blood screening for monoclonal immunoglobulin light chains. If a monoclonal protein is present, a bone marrow examination should be performed to evaluate for the presence of multiple myeloma. In a retrospective review of 100 known AL amyloid patients, bone marrow core biopsy revealed a plasma cell dyscrasia in 83 % (λ, 65; κ, 18) of cases [16]. Amyloid deposits were observed in 60 % of the bone marrow core biopsy specimens and, when present, were detected most often in blood vessel walls only (39 out of 60). Congo red staining of subcutaneous fat obtained by aspiration is a reliable and noninvasive test that positively identified amyloid deposits in 78 % of patients. If negative, a biopsy of the labial salivary glands may detect amyloid deposits in 50 % of patients. If this is also negative, then an involved organ should be biopsied when the clinical index of suspicion is high (see Fig. 14.4). Both IF and IHC staining are negative for intact immunoglobulin (Ig), but often positive for Ig light chain, which should be restricted to either of the two light chains (κ or λ). A limitation of IHC is reduced specificity due to background staining by normal light chain deposition. Another is the failure of commercial agents to detect the amyloid light chain because of conformational changes in the amyloid fibril that masks the relevant epitope. In one study, 12 of 34 patients (35.3 %) with known AL amyloidosis had negative IF staining for both κ and λ chains [17]. In contrast, AA amyloid is usually more accurately detected with standard antibodies against the AA protein.

The differential diagnosis of AL amyloid includes light chain deposition disease (LCDD). The amyloid deposits of LCDD are distributed in a uniform, granular pattern throughout the glomerulus and the tubular basement membranes. The PAS staining is much more intense than AL amyloid due to the inflammatory response stimulated by the light chain deposition. In AL amyloid the λ light chain isotype predominates, whereas in LCDD the κ isotype is more common. Given the lack of β-pleated fibril formation, LCDD does not emit apple-green birefringence.

Other considerations in the pathologic differential diagnosis of amyloidosis include fibrillary glomerulonephritis and immunotactoid glomerulopathy. In fibrillary glomerulonephritis, the morphologic appearance is indistinguishable from amyloid in that there is glomerular accumulation of nonbranching, randomly arranged fibrils. Like amyloid, there is often a lack of inflammatory cell infiltrate in the glomerulus. It differs from amyloid in that the fibrils are larger (usually 18–20 nm) and lack reactivity with Congo red and light chain IHC stains [18]. Immunotactoid glomerulopathy may be considered a subtype of fibrillary with similar morphologic and histochemical characteristics. However, this is a process where much larger fibrils (ranging from 34 to 49 nm) are deposited in an ordered and parallel orientation. An association with lymphoproliferative disorders has been identified.

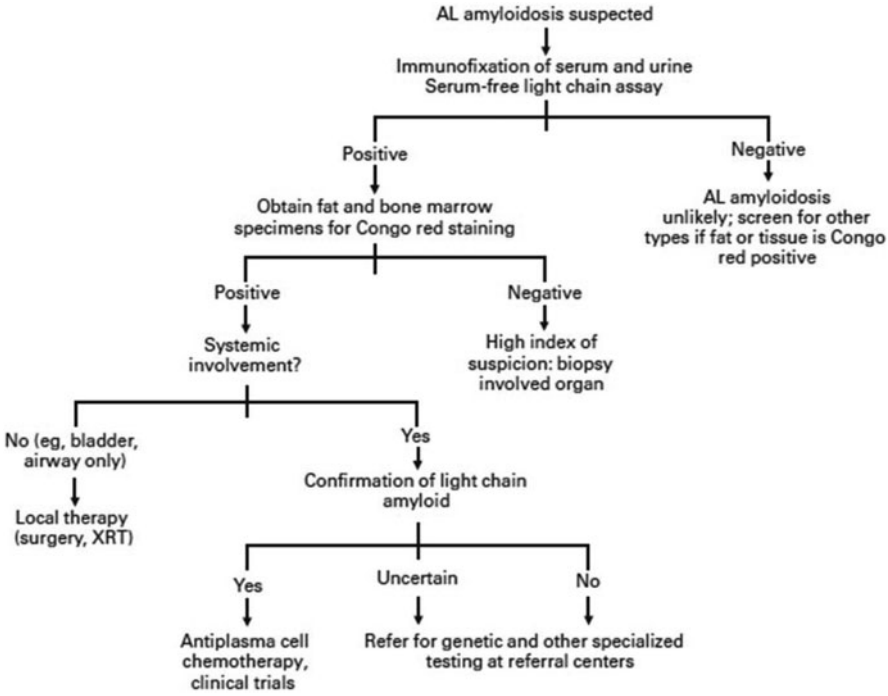

Fig. 14.4 Proposed diagnostic algorithm for AL amyloid. (Source: Reprinted with permission. © 2011 American Society of Clinical Oncology. All rights reserved. Merlini G: J Clin Oncol Vol. (29), 2011: 1924–1933)

It is now clear that an individual patient may have both a monoclonal gammopathy and a hereditary variant which creates the confounding scenario of two possible sources of the amyloid forming protein. AL amyloidosis often responds to chemotherapy that suppresses the underlying clonal plasma-cell disorder, but chemotherapy has no role in the treatment of hereditary amyloidosis and may be harmful. This was initially described in theUK where 350 patients with systemic amyloidosis in whom a diagnosis of sporadic AL amyloid was suggested by clinical findings (negative family history and the presence of a monoclonal gammopathy). However, DNA genotyping of whole blood for the most common causes of hereditary amyloidosis yielded mutations in 10 % of patients, most often in the genes encoding fibrinogen Aα and TTR [19]. Thus, in these cases the monoclonal gammopathy was considered incidental and these patients were not treated with chemotherapy. Since hereditary amyloid has variable penetrance, the family history proved to be an ineffective screening test. This series also revealed that in those patients with true AL amyloidosis, the Ig light chain fibrils were identified by IHC staining in only 38 % of the cases. This low value reflects the failure of anti-light chain antibodies to bind to light chain fragments once they have formed into an amyloid fibril. Thus, although IHC staining for amyloid forming proteins can be useful, protein- or DNA-based screening is recommended

due to the limitations of IHC. The Memorial Sloan Kettering group took a more targeted approach to hereditary screening for all patients referred for an evaluation of systemic amyloidosis. In their study of 178 patients, screening took place for those who met the following criteria: (1) asymptomatic African Americans were screened for the presence of a mutant TTR (the Val122Ile variant of TTR occurs in 4 % of African Americans); (2) patients with dominant peripheral nervous system involvement were screened for variants of TTR, apolipoprotein AI and AII, fibrinogen Aα, and lysozyme (peripheral neuropathy is a common presentation of AL amyloidosis and also several of the hereditary variants); (3) and patients with isolated renal amyloidosis and no amyloid in the bone marrow were screened for the fibrinogen Aα variant [20]. Of those who were screened, 6 % had both an incidental monoclonal gammopathy and a true hereditary amyloid protein identified in the same patient.

Because of sample size limitations of the tissue biopsy and the aforementioned limitations of IHC, a newer technique of LCM-MS-based proteomic analysis has been developed at Mayo Clinic to identify amyloid protein in both a specific and sensitive fashion. Laser capture microdissection (LCM) is used to specifically study those areas in the biopsy sample that are positive for Congo red staining, thus increasing the yield of the result. In brief, the process involves the microdissection of amyloid from the tissue biopsy. This is then digested into tryptic peptides and analyzed by liquid chromatography electrospray in tandem mass spectrometry (MS). The MS raw data files are queried by different computer algorithms to search protein databases for the compatible protein. A training set of 50 patients with cardiac amyloid was compared with the current gold standard approach (includes an extensive clinical investigation for plasma cell disorders, serum and genetic testing for amyloidogenic TTR variants, and IHC for TTR, SAA, Ig κ, Ig λ, and serum amyloid P component). This was later validated in 41 additional cases yielding a specificity of 100 % and sensitivity of 98 %, whereas IHC was comparatively informative in only 42 % [21, 22]. In a later study on amyloid diseases associated with neuropathy (includes AL, ATTR, AGel, and AApoAI), the specific amyloid subtype was identified in 21 different nerve biopsies by LCM-MS without assistance from clinical information [22]. In future, LCM-MS will likely become the new gold standard for identifying the protein forming the amyloid deposits when it becomes more generally available. However, there are limitations in LCM-MS, including that the mutations must be both known and available in protein databases and that the amino acid changes must lead to alterations significant enough to be detected by mass spectroscopy.

Non-AL Amyloid

Mutated genes that are associated with hereditary amyloid include apolipoprotein AI (Apo AI), TTR, fibrinogen Aα chain, lysozyme, cystatin C, gelsolin, and apolipoprotein AII. Each of them is associated with clinical amyloidosis syndromes and has distinct clinical manifestations such as age of onset, presenting signs, site of organ involvement, and rate of progression and prognosis. The most common clinical

manifestation of AApoAI is a slowly progressive, non-proteinuric renal failure due to tubular deposits of amyloid fibril. It is also associated with extensive deposits in the liver and spleen and no cardiomyopathy. The Gly26Arg mutation is most common among patients with Irish ancestry. Three Irish families were studied to assess the natural history of the disease and the usage of renal transplantation. As opposed to the generally rapid progression of renal failure seen in AL amyloid, the progression seen in AApoAI amyloid is slow. Renal failure usually presents as hypertension and mild proteinuria between age 18 and 55 years [23]. Histology demonstrated tubulointerstitial fibrosis with the unusual finding of amyloid deposition in the medulla. The UK study also supports the durable nature of renal transplantation in such patients. Over a median of 9 years from transplantation, eight of ten patients were alive, and seven with a functioning graft [24]. Renal transplantation may be used successfully to treat this disorder with uncommon failure of the graft due to amyloid recurrence. Patients who present with familial tubulointerstitial nephritis pattern and associated liver disease require a high index of suspicion for AApoAI amyloidosis.

Reactive systemic amyloidosis is comprised of the AA protein (SAA) secondary to an associated inflammatory condition. Examples of such disorders include rheumatoid arthritis, tuberculosis, chronic osteomyelitis, inflammatory bowel disease, and familial Mediterranean fever (FMF) [25]. The underlying disease causes chronically active inflammation. Of note, secondary amyloidosis can also occasionally occur in patients with neoplasms such as hepatocellular carcinoma, renal cell carcinoma, Castleman's disease, Hodgkin's disease, and hairy cell leukemia.

A process called "localized amyloid" may occur in individual organs, in the absence of systemic involvement. The reason for localized deposition is unknown, but it is hypothesized that the deposits result from local synthesis of the amyloid protein, rather than the deposition of light chains produced elsewhere. In a series of 20 cases of localized amyloidosis diagnosed between 1993 and 2003 in solitary organs involving skin, soft tissues, oropharynx, larynx, lung, bladder, colon, conjunctiva, and lymph nodes, no patient progressed to systemic disease over an average of 7 years [26].

Treatment

Case #2
Mr. P (from case #1) had an extensive pretreatment evaluation. He had a normal troponin but an elevation in N-terminal pro-brain natriuretic peptide (NT-pro-BNP) 467 ng/L. An echocardiogram showed a left ventricular ejection fraction (LVEF) of 54 % and mild concentric left ventricular hypertrophy with normal global left ventricular systolic function. He had a cardiac MRI which confirmed a normal left ventricular systolic function with an LVEF of 57 %. There was no

evidence of myocardial scar or infiltration suggesting that he had no amyloid involvement of his heart. He had an abdominal ultrasound which was negative for hepatosplenomegaly and a normal alkaline phosphatase suggesting no hepatic involvement. He had an excellent performance status. Thus, it was determined that Mr. P would be an appropriate candidate for treatment with high-dose melphalan followed by autologous hematopoietic stem cell transplantation (HSCT). Overall, Mr. P tolerated the treatment well over time and his proteinuria was reduced from > 5 to 1.5 g/day. His creatinine clearance remained stable. What clinical features in a patient with AL amyloidosis can predict outcomes?

a. Number of organs involved
b. Degree of cardiac involvement
c. Degree of renal involvement
d. Serum free light chains (FLCs)
e. Serum FLCs and degree of cardiac involvement

Early treatment intervention is critical in AL amyloid. Upon confirmation of the diagnosis, treatment should commence without delay given the progressive course of the disease. Delays in treatment can increase the number of organs involved or the severity of individual organ impairment. In turn, both factors will limit the available treatments, as patients with advanced single- or multiorgan involvement are less likely to tolerate aggressive regimens, such as high-dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT).

Treatment is divided into two broad categories, namely high-dose chemotherapy followed by autologous HSCT versus chemotherapy alone. To date, the literature remains mixed in definitively deeming one modality superior over the other. However, for reasons to be discussed below, HSCT remains the favored approach for most clinicians whenever feasible.

Stem cell transplant was first explored as a treatment option in the 1990s. The initial case series published in 1998 raised concern about high treatment-related mortality (TRM). Comenzo reported on a series of 25 patients with primary amyloidosis who were treated with dose-intensive intravenous melphalan followed by an autologous stem cell transplant. [27]. On an intention-to-treat basis, the 3-month mortality associated with therapy was 20 % (5 of 25). Two of the five patients had significant cardiac amyloid involvement and suffered sudden cardiac death [27]. Those with less than two organs involved, and those without cardiac involvement, faired significantly better than their counterparts with more extensive involvement. Moreau et al. reported similar findings in a series of 21 patients with systemic AL amyloidosis [28]. The conditioning regimen consisted of high-dose melphalan either alone or in combination with 12 Gy of total body irradiation [28]. Forty-three percent (9 of 21) of patients died within 1 month of transplantation. Patients with less than two organs involved had improved survival compared to those with more extensive organ involvement. Organ involvement was defined as creatinine clearance < 30 mL/min,

protein excretion > 3 g/24 h, congestive heart failure, neuropathy, or hepatomegaly associated with alkaline phosphatase level of > 200 IU/L.

Despite the high TRM of the earliest case series, a retrospective study suggested that there could be a benefit in overall survival and quality of life. One series included 126 patients, half of whom received HSCT and half of whom received chemotherapy alone. The groups were matched with respect to sex, age, left ventricular ejection fraction, interventricular septal wall thickness, peripheral nerve involvement, serum creatinine, and bone marrow plasmacytosis. The overall survival rates at 1 year were 89 % in the HSCT arm and 71 % in the chemotherapy arm, and 71 versus 41 % at 4 years [29].

Jaccard et al. conducted the only prospective randomized controlled trial that compared chemotherapy to autologous stem cell transplantation. One hundred patients were randomized to receive either melphalan and dexamethasone or high-dose melphalan followed by HSCT. The median survival in the melphalan plus dexamethasone arm was statistically significant longer at 56.9 months compared to 22.2 months in the arm receiving high-dose melphalan followed by stem cell transplantation [30]. Thus, the study failed to show a survival benefit in the transplantation arm. The results of this study should be interpreted with caution. There are limitations to the conclusions that can be drawn based on small number of patients included, the way the data was analyzed, and controversy regarding the selection criteria. From a statistical point of view, the data was evaluated using intention-to-treat analysis (ITT). In ITT, the analysis of results is based on the initial treatment assignment and not on the treatment eventually received in an effort to minimize artifact, such as nonrandom attrition from one arm, when interpreting the results. Of the 50 patients assigned to the stem cell transplant arm, 10 died prior to receiving this treatment. The majority succumbed to sudden death or progressive heart failure. In ITT analysis, these deaths were counted as mortalities in the transplant arm even though the patients never underwent transplantation. In a relatively small sample size, results can be profoundly altered by statistics of this kind.

This study highlights many issues surrounding AL amyloid and transplantation. Multiple myeloma and AL amyloid are both clonal plasma cell disorders and respond to similar treatments. The treatment of AL amyloid has been extrapolated from well-established treatments of multiple myeloma. However, the treatment-related toxicity is very different in both because of the pattern of end-organ damage. In multiple myeloma, patients have a significant burden of disease in the bone marrow but generally have well-preserved organ function with the exception of renal impairment [31]. In contradistinction, AL amyloid patients often have very little disease in the bone marrow with an average tumor burden of 5 % plasma cells [32, 33]. However, the burden of end-organ impairment is significantly higher. This results in starkly different treatment-related toxicity during stem cell mobilization and administration of high-dose chemotherapy.

The high number of deaths prior to transplant may reflect a liberal inclusion criteria for the Jaccard study when compared to other large centers treating AL amyloid [34, 35]. For example, over 84 % of the patients had two or more organs involved and over 25 % of the patients had New York Heart Association (NYHA) Grade III or IV heart

Table 14.2 Criteria for autologous stem cell transplant

Age ≤ 70 years
Troponin T < 0.06 ng/mL
NT-proBNP < 5000 ng/L
Creatinine clearance ≥ 30 mL/min (unless on chronic stable dialysis)
Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
NYHA functional status Class I or II
No more than two organs significantly involved (liver, heart, kidney, or autonomic nerve)
No large pleural effusions
No dependency on oxygen therapy
Adequate factor X levels

failure. The previously discussed retrospective studies and case series by Comenzo and Moreau demonstrate the importance of careful patient selection when considering transplant. These early studies strongly suggest that patients with extensive organ involvement and/or severe cardiac impairment fair significantly worse and should probably be excluded from transplant due to high TRM [27, 28]. The TRM in the transplant arm of the Jaccard study was 24 % which is double the rate of what had previously been reported in single-center studies [28, 34, 36–38]. Gertz et al. reported that at the Mayo clinic there was a 40 % reduction in TRM after 2006, which is largely attributed to improved selection criteria [31]. Thus, in the prospective randomized trial by Jaccard, the benefit of transplant may have been masked by inappropriate patient selection.

The considerable heterogeneity in the prognosis of AL amyloid depends on the number and degree of organs involved. At present, the patients must satisfy the criteria listed in Table 14.2 to be eligible for transplant [39–41]. Multiple studies have validated these criteria in the selection of patients [28, 42–45]. The degree of cardiac impairment, as measured by troponin and NT-pro-BNP is the most potent predictor of outcome [46, 47]. Both values have been incorporated into the Mayo stage and the revised Mayo stage. The Mayo stage is obtained information from 242 patients newly diagnosed with AL amyloidosis [48]. Patients were stratified into three groups based on NT-pro-BNP and troponin T levels. Stage I is defined as Cardiac troponin < 0.035 mcg/L and NT-proBNP < 332 ng/L. Stage II is defined as elevation in one value, either the troponin or NT-proBNP being above the defined threshold values. Stage III is defined as both values being above the threshold values. The median survival is 26 months in stage I, 11 months in stage II, and 4 months in stage III. The staging was also applied to patients receiving stem cell transplant. Of note, patients with stage III disease had less than a 12-month survival even with transplantation [49]. The Revised Mayo staging adds serum FLC and uses different cutoff values of NT-pro-BNP and Troponin T levels to improve risk stratification [50]. As with the original Mayo stage, those with more advanced stages have a poorer prognosis both with and without transplantation.

Case #2 Follow-up and Discussion
Based on the revised Mayo staging, serum FLCs and cardiac involvements are the most important predictors of outcomes. Choice e is correct.

In summary, many questions remain regarding the utility of stem cell transplantation in AL amyloid. More studies are needed using the now widely accepted eligibility criteria to best select AL amyloid patients for transplant. It also remains to be seen what role transplantation will play as newer immunomodulatory agents and proteasome inhibitors come into use. For example, Dispenzieri et al. reported that in a group of transplant eligible patients who opted for chemotherapy alone the median survival was 42 months, a number which rivals the results seen with transplant [51]. Future studies will need to examine the role of autologous stem cell transplant in the setting of newer chemotherapeutic agents.

Melphalan and Dexamethasone

Case #3
Mr. C is a 76-year-old man who presented to his primary care physician with the complaint of "foamy urine." He had a normal creatinine. A 24-h urine collection revealed 4.9 g of proteinuria. Serum and urine immunofixation revealed λ type Bence Jones protein. FLCs λ were elevated at 23.6 mg/dL (reference range 0.57–2.63 mg/dL). The κ/λ FLC ratio was 0.08 (reference range 0.26–1.65). He had a kidney biopsy which showed AL amyloid, λ light chain with mild to moderate involvement of glomerular and arterial vessels. A bone marrow biopsy followed which showed a λ-restricted plasma cells and amyloid in the vessel walls. What is the best treatment option for this patient?
a. Bortezomib
b. Melphalan and dexamethasone
c. High-dose chemotherapy followed by stem cell transplantation.

Patients who are ineligible for HSCT due to the severity of organ involvement are precisely the patients who require an effective treatment that provides a rapid response to stabilize or reverse the progression of their disease. Borrowing from the experience with multiple myeloma treatments, several studies examined melphalan and prednisone [52, 53]. Melphalan acts by alkylating DNA bases and cross linking DNA strands, which results in DNA fragmentation due to impaired repair, prevention of DNA synthesis or transcription, and the induction of mispairing of the nucleotide leading to mutations.

In two randomized controlled studies, melphalan and prednisone were superior to colchicine [53, 54]. Importantly, melphalan seemed to be effective and safe in patients with cardiac impairment [55]. This is significant because, as previously discussed, cardiac impairment is a major prognostic indicator as well as a major predictor for TRM and morbidity. The response rate for melphalan and prednisone was 28 % and the time to response was protracted with 70 % of patients experiencing a response in 1 year and an additional 20 % requiring 2 years to show a response to therapy. Based on the Mayo staging and the revised Mayo staging, previously discussed, only patients with stage I disease have a median survival of more than 2 years. Thus, many AL amyloid patients will not live long enough to see a benefit from treatment that requires up to 24 months to reach its maximum effect. For this reason, alternative regimens were explored in the hopes of achieving a brisker response.

In 2004, Palladini et al. reported the results of a prospective study including 46 HSCT- ineligible patients who received treatment with melphalan and dexamethasone [56]. The overall response rate in this study was 67 %, with nearly half of the patients demonstrating an improvement in organ function. Importantly, the response to treatment was both brisk and durable with a median time to response of 4.5 months and an overall survival of 5.1 years [56]. In addition, the combination was safe with only 4 % TRM [56]. A prospective study of 159 HCST-ineligible patients treated with melphalan and dexamethasone, also reported by Palladini, showed both a favorable hematologic and organ response, in 62 and 35 % of patients, respectively [57]. Conversely, two later studies, also with melphalan and dexamethasone, showed a dismal median survival of less than 18 months [58, 59]. The incongruity of these two studies is attributed to the severe cardiac impairment of the included patients. For example, 82 % of the patients in one study had NYHA Class III or IV heart failure [59]. These results highlight two recurrent themes in the amyloid literature, namely that patients with severe cardiac impairment have significantly poorer outcomes, and that it is difficult to compare treatments across studies when the eligibility criteria is discordant.

Nevertheless, melphalan and dexamethasone are still considered as a standard treatment in the transplant-ineligible population. It is an oral regimen which is well tolerated in all but those with the severest of cardiac impairment and it can induce hematologic and organ responses even in patients with advanced disease [60]. Melphalan is associated with mild GI side effects which are generally controlled with antiemetics and supportive care. Hematologic toxicity is another common side effect which may be dose limiting [61].

Case #3 Follow-up and Discussion

Given his age, he was not a candidate for high-dose chemotherapy followed by stem cell transplant. He was treated with 4 days of melphalan 0.22 mg/kg and dexamethasone 40 mg every 4 weeks. He received six cycles and his 24-h urine protein decreased to 1442 mg and free lambda light chain improved to 9.3 mg/dL. Hence the correct answer is b.

In regard to renal function and oral melphalan, there is no clear consensus on dosing. For patients treated with high-dose intravenous melphalan and HSCT, therapy-related toxicity is proportional to the renal dysfunction. However, even in patients on dialysis, treatment with high-dose melphalan is feasible provided it is dose-adjusted [62]. It is unclear whether the lower dose oral melphalan used in the melphalan and dexamethasone regimen should also be adjusted based on renal function. In a retrospective analysis of 272 patients treated with oral melphalan at 25 mg/m^2, hematologic toxicity was significantly increased in patients with a creatinine clearance of < 30 ml/min. More than a third of these patients experienced hematologic toxicity of WHO $\geq$ grade 3. However, this did not translate into a significant increase in severe infection and bleeding [63]. While acknowledging the lack of clear data, Carlson et al. recommended a dose reduction of 25 % in patients with a creatinine clearance of < 30 ml/min, given the potential risk of neutropenia and thrombocytopenia. In this study only 2 % of the patients had a creatinine clearance of < 10 ml/min, thus no specific recommendations could be made for this subgroup [64].

Novel Agents in the Treatment of Amyloid: Immunomodulators and Proteasome Inhibitors

In the hope of improving upon the speed and depth of response, other classes of medications have been explored. The immunomodulators, including thalidomide and its analogues lenolidomide and pomolidomide, and the proteasome inhibitor bortezomib are of particular interest because of their efficacy in multiple myeloma. Both classes target multiple pathways involved in cell proliferation. The immunomodulators have several potential mechanisms of action in AL amyloid. They are known to alter cytokine secretion, modulate T-lymphocytes, inhibit angiogenesis, and alter expression of adhesion molecules. Any combination of these mechanisms may be responsible for their clinical efficacy in AL amyloidosis [65]. The proteasome inhibitor bortezomib binds with high affinity to the catalytic site of the 26S proteasome [66]. In normal cells, the proteasome degrades ubiquitinated proteins and also removes abnormal or misfolded proteins. Cancer cells often have both higher levels of proteasome activity and are more sensitive to the pro-apoptotic effects of proteasome inhibition [67]. The literature involving the use of immunomodulators, bortezomib, and other novel agents in the treatment of AL amyloid is reviewed below.

a. Thalidomide
   Given the frequency of renal involvement in AL amyloid patients, thalidomide is particularly attractive because it does not require dose adjustment for renal impairment or dialysis and it has minimal hematologic toxicity [68]. However, thalidomide does carry a black box warning for birth defects and venothromboembolic events [69].
   The data with single agent thalidomide have been disappointing. In 2003, Seldin et al. reported the results of 16 patients treated at a median dose of 300 mg/day,

none achieved organ responses [70]. In a subsequent phase II study using higher doses of thalidomide, higher response rates were seen at the cost of significantly increased treatment-related toxicity [71]. Approximately 75 % of patients experienced progressive edema, cognitive difficulties, and constipation. Progressive renal insufficiency due to disease progression was seen in 42 % of patients. All 12 patients had withdrawn from the study at the time of publication, with 50 % of the patients withdrawing due to side effects and the remaining due to progression or death [71].

In hopes of improving outcomes, a combination of low dose thalidomide with dexamethasone was explored in patients with refractory or relapsed AL amyloidosis. Thalidomide was initiated at 100 mg/d, with 100-mg increments every 2 weeks, up to 400 mg. Dexamethasone was given at 20 mg daily on days 1–4 [72]. The cycle was repeated every 3 weeks. The combination resulted in improved hematologic response in 15 out of 31 (48 %) with 6 out of 31 (19 %) complete remissions, and 8 out of 31 (26 %) organ responses. Furthermore, the median time to response was fairly brisk with a mean of 3.6 months (range, 2.5–8.0 months) [72]. As with the previous study, there was significant treatment-related toxicity in 65 % of the patients, with 25 % experiencing symptomatic bradycardia. Only 35 % patients tolerated the 400 mg/d thalidomide dose [72]. Thus, low dose thalidomide and dexamethasone could be considered as second line treatment.

In a 2007 study by Wechalekar, 75 patients with AL amyloidosis received the combination of cyclophosphamide, thalidomide, and dexamethasone (CTD regimen) dose adjusted for age and cardiac dysfunction. An attenuated CTD regimen (CTDa) was given to those over the age of 70, or with heart failure, or signs of significant fluid overload. Each cycle of CTDa lasted 28 days [73]. Both regimens included low dose thalidomide at 100 mg/day. A hematologic response occurred in 48 (74 %) of 65 evaluable patients, including complete responses in 14 (21 %) and partial responses in 34 (53 %) cases. Three-year estimated OS was 100 % and 82 % among complete and partial hematologic responders, respectively. These response rates were higher than any previously reported non-transplant regimen for AL amyloidosis. As compared with previous studies, treatment-related toxicities were improved, but still present. Toxicity necessitating cessation of therapy occurred in 8 % and was at least grade 2 in 52 % of patients. TRM was 4 % [73]. When taken as a group, these studies suggest that thalidomide, particularly in combination with other agents, has activity in AL amyloid. However, given its associated treatment-related toxicity, other regimens are preferentially used.

b. Lenalidomide

Lenalidomide, a newer analogue of thalidomide, is associated with better toxicity profile and thus represents a more feasible treatment option. In contrast to thalidomide, it must be dose reduced in the setting of renal dysfunction and in dialysis patients. The pharmokinetics of lenalidomide were examined in a study of 30 patients between the age of 39 and 76 [74]. Based on this study, 40–60 % dose adjustments are required for patients with a creatinine clearance of less than 50 mL/min. In patients with a creatinine clearance of less than 30 mL/min, both a dose reduction of 60 % and extended dosing interval of 48 h are recommended.

For patients on dialysis, the dosing interval should be extended to three times per week at 60 % dose reduction [74].

Despite improved toxicity profile as compared to thalidomide, AL amyloid patients do experience greater toxicities with lenalidomide when compared to patients with multiple myeloma treated with the same dose [75]. Common adverse reactions include peripheral edema, fatigue, fever, and cytopenias. GI disturbances including nausea, vomiting, diarrhea or constipation, and anorexia are also frequently reported [76].

Two studies have evaluated the efficacy of lenalidomide (initial dose 25 mg/day PO for 21 days of a 28-day cycle) with or without dexamethasone in patients with AL amyloid [59, 60]. Overall response rates for subjects taking both medications were 67–75 %, with complete responses in 16 % [58]. In one of the studies, organ responses were seen in 42 % of patients who received at least three cycles of therapy [59].

c. Pomalidomide

Pomalidomide, the latest analogue of thalidomide, is currently under investigation for the use in light chain amyloidosis. There is limited clinical experience with this agent, and appropriate renal dosing has not been firmly established. At present, it is not recommended for use in patients with a serum creatinine of greater than 3.0 mg/dL.

In 2012, the results of a prospective phase II trial using pomalidomide and dexamethasone in previously treated AL amyloidosis patients were reported. In this study, oral pomalidomide and dexamethasone were administered to 33 patients. The confirmed hematologic response rate was 48 %, with a median time to response of 1.9 months. Organ improvement was documented in five patients [77]. There are three registered clinical trials examining the use of pomalidomide in AL amyloidosis, two in the first line and one in the second line setting (NCT01510613, NCT01728259, and NCT01807286) [78]. The data are still pending whether pomalidomide is less toxic or more efficacious than the other thalidomide analogues.

d. Bortezomib

As with thalidomide and its analogues, the success of bortezomib in multiple myeloma prompted evaluation of its use in the treatment of AL amyloid [79]. Bortezomib does not require dose adjustment in renal impairment. Since dialysis may reduce the plasma concentration, post-dialysis administration is recommended [80]. It is the preferred agent in patients with renal failure. Bortezomib's side effects include fever, fatigue, and cytopenias. Bortezomib is associated with peripheral neuropathy which can be minimized by using subcutaneous administration or weekly dosing [76].

Two retrospective studies examined the use of bortezomib in combination with cyclophosphamide and dexamethasone (CyBorD) [81, 82]. In a single center retrospective analysis of 43 patients, the overall response rate was 81 % with 42 % of patients achieving a complete response [81]. In another retrospective analysis examining CyBorD in 17 patients, 16 patients demonstrated a hematologic

response and 12 of those responses were complete [82]. Perhaps even more significant, the median time to response was 2 months. In addition, after treatment with bortezomib, three patients became eligible for stem cell transplant.

In 2011, the results of the first prospective phase II trial of single-agent bortezomib in relapsed primary systemic AL amyloidosis were reported. The dosing consisted of 1.6 mg/m^2 on days 1, 8, 15, and 22 every 35 days or 1.3 mg/m^2 twice weekly on days 1, 4, 8, and 11 every 21 days. Seventy patients were enrolled in the study. The hematologic response was similar in both arms at 68.8 and 66.7 %, in the 1.6 and 1.3 mg/m^2 arm, respectively. Among all 70 patients, organ responses included 29 % renal and 13 % cardiac responses. [83].

As with the previous studies, the time to response was shorter when compared to lenalidomide and thalidomide, with the median time to first response ranging from 0.7 to 2.1 months in these two studies. Importantly, outcomes appeared similar in patients with cardiac involvement. As with lenalidomide and thalidomide, there was significant treatment-related toxicity. Grade 3 or greater toxicity was reported in 79 % of the patients and 53 % of the patients had to discontinue the medication [83]. The Grade 3 toxicities included neuropathy, fatigue, thrombocytopenia, and GI upset.

Two studies examined the benefits of bortezomib combination chemotherapy. A multicenter prospective European study included 428 previously untreated patients with primary AL amyloidosis. In this study, the patients were separated into five treatment arms consisting of various combinations of agents including melphalan, cyclophosphamide, bortezomib, thalidomide or lenalidomide, and dexamethasone [84]. There was a median reduction of 91 % FLC levels after treatment with bortezomib–dexamethasone [84]. Organ response was not reported, likely because this is a delayed endpoint. While hematologic response is significant, it does not necessarily translate into organ response and the full clinical significance of bortezomib remains unknown. In addition, case reports of acute cardiac failure have been reported with bortezomib [85, 86]. This study did not report cardiac biomarkers on the included patients. The patients in this study were previously untreated and carried a diagnosis of AL amyloid for an average of 32 months upon at the time of enrollment. Thus it is postulated that the patients included in this study may have had minimal cardiac impairment, since those with significant cardiac involvement would not be expected to survive so long without the benefit of treatment.

A clinical trial (NCT01078454) randomizing previously untreated patients between treatment arms with a melphalan–dexamethasone and a melphalan–dexamethasone–bortezomib recently closed [78]. The results are pending. It will be interesting to see if bortezomib′s role in combination therapy is confirmed in this study.

Response Assessment

Case #4
Mr. C (from Case #3) was monitored and his disease remained stable for some time. However, approximately 2 years after completing the treatment with melphalan and dexamethasone he was noted to have a consistent rise in both λ FLC and 24-h urine protein, which reached 42.4 mg/dL and 3123 mg, respectively. Given progression of the disease, it was decided to commence treatment with subcutaneous bortezemib 1.3 mg/m^2 and dexamethasone 40 mg weekly for 4 weeks followed by 1 week off. What is the best way to monitor response in Mr. C?
a. Serum FLC ratio
b. Serum FLC difference
c. 24-h urine protein excretion

Regardless of whether a patient receives only chemotherapy or high-dose chemotherapy followed by hematopoietic stem cell transplant, determining the response to treatment is imperative since it correlates with overall survival. There are two components, a hematologic response and organ response. Hematologic response is determined by FLC levels and ratio in addition to serum and urine immunofixation. FLC levels represent the amount of kappa and lambda in the serum. Lambda light chains circulate as dimers, slowing their clearance and increasing their half-life. Therefore, serum concentrations of lambda are greater than kappa, and the median ratio in published series is less than 1.0. Increased concentrations of kappa and lambda with a normal ratio are typical of patients with polyclonal gammopathy or impaired renal function, while abnormalities in the ratio point toward a monoclonal gammopathy. Complete hematologic response is defined as normalization of FLC level and ratio as well as negative serum and urine immunofixation. Other degrees of hematologic response are listed in Table 14.3. Hematologic response is important because it precedes and correlates with organ response. Thus, hematologic response can provide early insight into the patient's prognosis. Of all the response criteria, a 90 % reduction in serum FLC correlates with improved survival [87]. Polyclonal serum FLC concentrations increase as kidney disease worsens. This limits the ability to monitor monoclonal light chain by FLC measurement alone. In a study from the Mayo clinic, the monoclonal component of FLC was estimated by subtracting the concentration of the uninvolved light chain from that of the amyloidogenic light chain to obtain the FLC difference (dFLC). This strategy of measuring dFLC has been validated in previous multiple myeloma studies [88].

Organ response criteria are established for the heart, kidney, liver, and peripheral nervous system. They are listed in Table 14.4 [89]. In a multicenter series of 816 patients followed for 4 years, cardiac response in terms of NT-pro-BNP levels was

Table 14.3 Hematologic response in AL amyloid

CR	Normalization of FLC level and ratio, negative serum, and urine immunofixation
VGPR	Reduction in difference between involved FLC and uninvolved FLC (dFLC) to < 40 mg/dL
PR	A greater than 50 % reduction in dFLC
No response	Less than a PR
Progression	FLC increase of 50 % to greater than 100 mg/L
	If previously in CR Any detectable M protein or FLC ratio with doubling of light chain
	If previously in PR 50 % increase in serum M protein to 0.5 g/dL or 50 % increase in urine M protein to 200 mg/day

CR complete response, *VGPR* very good partial response, *PR* partial response, *FLC* free light chain, *dFLC* free light chain difference

Table 14.4 Organ response

Heart	Mean interventricular septal thickness decreased by 2 mm, 20 % improvement in ejection fraction, improvement by two NYHA classes without an increase in diuretic use, and no increase in wall thickness
Kidney	50 % decrease (at least 0.5 g/day) of 24-h urine protein (urine protein must be 0.5 g/day pretreatment) Creatinine and creatinine clearance must not worsen by 25 % over baseline
Liver	50 % decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm
Nerve	Improvement in electromyogram nerve conduction velocity (rare)

highly correlated with overall survival [90]. There is some controversy surrounding the most accurate assessment of kidney response. The included guidelines define a kidney response as a 50 % decrease in urine protein when the pretreatment protein is > 0.5 g/day. Serum creatinine and creatinine clearance must not worsen by more than 25 %. However, in a retrospective analysis of 141 patients who underwent an autologous transplant and were followed for over 4 years urinary protein and serum creatinine did not seem to be as potent predictors of outcome [91]. Survival rates were similar in patients who achieved a 50–75 % reduction in 24-h urine protein loss when compared to patients who achieved less than a 50 % reduction. In addition, an increase in serum creatinine of 25 % or greater did not translate into worse outcome provided the patients did have > 75 % reduction in proteinuria [91]. Thus, it is debatable whether serum creatinine is an independent prognostic factor.

Case #4 Follow-up and Discussion
Mr. C's λ FLC improved to 9 mg/dL and the 24-h urine protein decreased to 67 mg/dl. Both serum FLC ratio and difference as suggested above might be good ways to evaluate response.

A Focus on Renal Outcomes in AL Amyloid: Prognostication, Dialysis, and Renal Transplant

In 2011, Pinney et al. analyzed the clinical outcome of 923 consecutive patients with renal AL amyloidosis who were observed at a single national center over a period of 21 years.

Renal involvement in AL amyloidosis was defined as proteinuria of more than 0.5 g/d according to the amyloidosis international consensus criteria [89, 92]. Risk factors for progression to dialysis were analyzed among 752 patients with a baseline estimated glomerular filtration rate (eGFR) of ≥ 15 mL/min. Among the 752 patients, 98 (13.0 %) experienced progression to ESKD and received dialysis after a median time of 26.8 months from diagnosis. Independent factors at baseline associated with progression to dialysis were higher chronic kidney disease (CKD) stage and lower serum albumin. FLC response was also significantly associated with progression to dialysis; patients with a 50–90 % response and patients with a more than 90 % response were less likely to experience progression to dialysis compared with patients with less than 50 % response.

A separate analysis of predictive factors for renal progression and renal response was undertaken in all 429 patients with adequate follow-up renal data. Renal progression was defined as the earliest of the following: starting dialysis; 50 % increase in proteinuria and increase by ≥ 1 g/d; or 25 % increase in serum creatinine and follow-up creatinine more than 1.20 mg/dL [89]. Renal response was defined as the earliest of the following: 50 % decrease in proteinuria and decrease by ≥ 0.5 g/d as long as creatinine had not increased by 25 %; or 25 % reduction in serum creatinine as long as proteinuria had not increased by 50 % [89]. Among the 429 evaluable patients, progression of renal disease from baseline occurred in 235 patients (54.8 %), and renal responses occurred in 140 patients (32.6 %). The median time to progression in the 54.8 % of affected patients was 23.8 months. Interestingly, CKD stage at baseline did not significantly influence chance of renal response, with approximately 30 % of patients in CKD stages 1 to 4 achieving a renal response. Factors associated with an increased risk of renal progression in univariate analyses included: poor FLC response at 6 months, high 24-h urine protein, and low serum albumin. Conversely, achieving more than 90 % FLC response at 6 months was associated with an almost fourfold increase in the chance of renal response ($P < .001$) and a 68 % reduction in the chance of renal progression ($P < .001$) when compared with an FLC response of 0–50 %.

Two hundred twenty-one (23.9 %) of 923 patients with renal AL amyloidosis required dialysis during the course of their disease. One hundred fourteen (51.6 %) dialysis-dependent patients died. Serum albumin < 2.5 mg/dL ($P < .04$) and alkaline phosphatase > 130 U/L at the start of dialysis ($P < .02$) were significantly associated with mortality. The median survival time from commencement of dialysis was 39.0 months. This is a considerably longer survival than previously reported [93–96]. The survival on dialysis was 43.6 months for patients starting after 2002. The authors postulate that the prolonged survival on dialysis compared with other series likely reflects a combination of improved supportive care, improved dialysis techniques, and better chemotherapy treatments for AL amyloidosis.

While the improved survival is encouraging, it should be noted that other studies have established that AL amyloid patients tend to have a shorter survival on dialysis than patients with AA amyloid. In 2008, Bollée et al. reported on the survival of 39 patients with either AA (20 patients) or AL amyloid (19 patients) who were undergoing dialysis [96]. Bollée concluded that while the outcomes were slightly better than those previously reported, patients with AL amyloid on dialysis had a significantly shorter survival than patients with AA amyloid. The median survival for AL amyloid patients was 26 months while that for AA amyloid patients was not definable given their extended survival. Risk factors for death at 1 year for the patients in this study included AL amyloid subtype, cardiac amyloidosis, heart failure, and shorter time from diagnosis to dialysis. In another retrospective study which included both AL and AA amyloid patients on dialysis, Moroni reported the best outcomes in patients without cardiac involvement on 2D-echocardiography [97].

AL amyloidosis excludes a patient from consideration for renal transplantation in some centers given the systemic nature of the disease and the concern for allograft failure from amyloid recurrence. In the large series by Pinney, less than 10 % of patients reaching ESKD underwent renal transplantation. Selection criteria for renal transplantation included absence of overt myeloma, a hematologic response to chemotherapy sufficient to prevent amyloid accumulation by serial SAP scintigraphy, and little or no clinically significant extrarenal amyloidosis, as well as willingness of the center to list the patient. In this small group of highly selected patients, the median estimated survival time from renal transplantation was 89.0 months. In this series, there was not a single graft loss from recurrent AL amyloid and all deaths occurred in the setting of a functioning renal allograft. These findings suggest that patients without extrarenal AL amyloidosis who have achieved a good hematologic response should be considered for renal transplant.

The role of autologous stem cell transplant in patients with ESKD on hemodialysis has also been explored. In 2003, Casserly et al. reported on 15 patients with AL amyloidosis-associated ESKD who were treated with intravenous melphalan (70–200 mg/m^2) and autologous peripheral blood stem cell transplantation. Treatment outcomes and toxicities were compared with 180 non-ESKD patients treated during the study period. Eight of 15 patients (53 %) had a hematologic complete response following treatment. Two patients (13 %) died during the peritransplant period. Transfusion requirements were greater and mucositis was more severe in the ESKD patients compared with the non-ESKD patients. Median survival for the ESKD patients with a hematologic complete response was 4.5 years. At the time of

publication, five patients with hematologic complete response had either undergone or were awaiting renal transplantation. This small series while by no means definitive, again suggests that for a highly selected group of patients with ESKD, autologous transplant may be feasible and may provide a bridge to renal transplantation.

Many patients with AL amyloid have renal involvement which makes them ineligible for high-dose chemotherapy followed by autologous stem cell transplantation because of unacceptably high TRM as previously discussed. In 2005, Leung et al. explored the issue of renal transplant in the AL amyloid patient from a different angle. A series of eight patients treated at the Mayo Clinic received a living donor kidney transplant followed by autologous stem cell transplant [98]. Leung postulated that restoring adequate renal function with a living donor transplant might allow these patients to proceed to autologous stem cell transplant with reduced risk of complications. Five of the eight patients who received a living donor kidney transplant had successful autologous stem cell transplantation. At follow-up, ranging from 0.4 to 2.3 year post-stem cell transplantation, renal function was adequate in the five survivors who underwent both procedures (serum creatinine concentration ranging from 0.9 to 1.9 mg/dL). The small number of patients studied and the relatively short follow-up time makes these results difficult to apply broadly. However, it does suggest that for carefully selected AL amyloid patients renal transplant followed by autologous stem cell transplant may be feasible and beneficial. The use of renal transplantation in non-AL amyloid is discussed earlier.

Summary

Significant advances have been made in the diagnosis and characterization of amyloid. LCM-MS has allowed for sensitive and specific typing of amyloid. AL amyloid remains an uncommon disease with an often systemic presentation. As diagnostic accuracy improves, AL amyloid patients will be identified earlier in the course of their disease allowing for a broader range of treatment options including high-dose chemotherapy followed by autologous HSCT. Early studies have clearly demonstrated that patients need to be stringently selected for autologous HSCT to minimize TRM and to maximize the clinical benefit. The investigation of newer immunomodulators, proteosome inhibitors, and novel agents will likely lead to deeper responses to treatment with improved side effect profiles. It will require continued collaboration both across treatment centers and across disciplines, particularly between nephrologists and hematologists, to best advance the care of AL amyloid patients.

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Chapter 15
Obstructive Renal Disease in Cancer Patients

Ala Abudayyeh and Maen Abdelrahim

List of Abbreviations

AKI	Acute kidney injury
ALL	Acute lymphocytic leukemia
AQP	Aquaporin
CT	Computed tomography
GFR	Glomerular filtration rate
HSCT	Hematopoietic stem cell transplantation
MRI	Magnetic resonance imaging
PCN	Percutaneous nephrostomy
RTA	Renal tubular acidosis
UTO	Urinary tract obstruction

Case #1
A 45-year-old male presented to the emergency room with increasing abdominal distention, pain, and decreased urinary output. He underwent a computerized axial tomography (CAT) scan without contrast due to his elevated serum creatinine at 5 mg/dl (eGFR 12.6 ml/min/1.73 m^2). CAT scan indicated bilateral hydronephrosis with a large mass compressing both ureters. Serum sodium was 131 mg/dl, and bicarbonate was 20 mg/dl. Vital signs showed a blood pressure of 150/80 mm/Hg and a heart rate (HR) of 80/min. In addition,

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he had decreased breath sounds in lower lung fields and abdominal distention with no shifting dullness. Urine analysis was significant for multiple hyaline casts. He underwent computed tomography (CT)-guided biopsy of the mass which was positive for large B cell lymphoma. What would be next step of management?

a. Bilateral ureteral stenting
b. Bilateral nephrostomy tubes
c. Intravenous hydration only
d. Initiate chemotherapy for the underlying malignancy

Acute kidney injury (AKI) in the cancer population continues to be a challenge. The culprits for AKI are most commonly associated with prerenal causes such as hypovolemia due to chemotherapy-induced nausea, vomiting, diarrhea, and severe mucositis. Intrinsic renal injury associated with the nephrotoxic chemotherapies is another common cause of AKI. In addition, chemotherapy toxicities and AKI interaction can set up a vicious cycle. Therefore, identifying even partial obstruction of urinary tract (UTO) contributing to AKI especially in solitary kidneys is very important. In many instances, it is a potentially reversible cause of acute renal failure in cancer population. In addition, reduced glomerular filtration rates (GFR) would exclude patients from curative stem cell transplantation or clinical trial drugs because of the increased mortality associated with renal failure. Therefore, early detection and treatment of obstruction in a cancer population will allow the administration of full dose of needed therapy for the underlying malignancy.

Etiology

Urinary obstruction is most commonly associated with tumors of rectal, bladder, prostate, or gynecology organs. Metastatic spread of tumors that originate from outside the pelvis, such as breast, pancreatic, and gastric cancers, can infrequently cause UTO. In bladder cancer setting, obstruction can be intrinsic to the kidney such as transitional cell carcinoma, blood clots, deposition of crystals (uric acid, acyclovir, methotrexate) or casts (multiple myeloma) within the tubules that block urine flow, or it can be ureteral distal to renal pelvis caused by transitional cell carcinoma, external compression caused by tumors, enlarged lymph nodes, blood clots, secondary retroperitoneal fibrosis (carcinoid, Hodgkin's and non-Hodgkin's lymphoma, (AA) amyloidosis, sarcomas, colorectal, breast, prostate, and bladder carcinoma, radiation therapy for testicular seminoma, colon, pancreatic cancer).

Again, at bladder level, obstruction is present related to outlet obstruction from bladder cancer or bladder atony due to chronic cystitis (i.e., infections) or radiation induced. Obstruction post-bladder can commonly related to prostate cancer or urethral strictures. The obstruction can of course be unilateral, bilateral, partial, or complete.

BK virus is an important cause of obstruction in cancer patients. BK belongs to the genus *polyomavirus hominis 1* of the family *Polyomaviridae*, which is of nonenveloped virions with icosahedral capsids with a 40-nm diameter that enclose the small circular double-stranded DNA genome of 5 kb. BK virus causes infection in genitourinary tract, due in part to its tropism for genitourinary epithelium. BK related UTO have been reported in kidney transplantation and reported to occur in approximately 3 % of allograft recipients [1]. In cancer patients, BK infection occurs after stem cell transplantation and manifest as inflammation and hemorrhage in urinary tract especially in bladder causing UTO [2]. In hematopoietic stem cell transplant (HSCT), recipient's BK virus infection leads to prolonged hospital stay and increased mortality secondary to the late hemorrhagic cystitis, ureteral stenosis, and nephropathy [3, 4]. Post HSCT-related BK nephritis is discussed in detail elsewhere in this book.

Pathophysiology

Due to obstruction, there is an increase in pressure proximal to the obstruction maintaining the GFR [5]. The rise in proximal pressure is eventually responsible for the dilatation of the collecting system. Due to the high intraglomerular pressure, there is a negative feedback to the proximal tubule to lower the GFR. In addition, there is a secondary renal vasoconstriction and reduction in glomerular blood flow, which is induced by an increase in angiotensin II, thromboxanes, vasopressin, and 20-HETE and decrease in nitric oxide and bradykinins. The end result is decreased renal blood flow and GFR in a setting of prolonged obstruction [6]. Acute tubular necrosis ensues due to increase in inflammatory cells infiltration in setting of obstruction. Monocytes and macrophages release transforming growth factor-beta (TGF-beta) and other cytokines, proteases, and oxygen free radicals that may contribute to tubular injury and fibrosis. It has been shown that removal of the immune cell infiltrate in ureteral obstruction by irradiation markedly improves glomerular filtration rate and renal blood flow, and partially corrects sodium and water excretion [7]. This combined injury, if prolonged, leads to irreversible injury. Renal recovery will usually start in the first 7–10 days after relief of obstruction. Selective decrease in urinary aquaporin 2 (AQP2) and increase in prostaglandin E2 excretion in post-obstructed kidney leads to polyuria (Fig. 15.1). The most common electrolyte abnormalities associated with ureteral obstruction are hyponatremia and hyperkalemia secondary to reduction in the amounts of both luminal Na-K-2Cl co-transporter and basolateral Na-K-ATPase in medullary thick ascending limb of the nephron respectively [8] (Fig. 15.1). Distal renal tubular acidosis (RTA) with hyperkalemia has also been reported with UTO. In addition, acidification defects due to loss of the lumen-negative potential difference due to reduced activities of transporter proteins, such as apical Na-K-2Cl cotransporters, sodium channels, and basolateral Na-K-ATPase can occur. Aldosterone resistance and or hypoaldosteronism [9] has also been reported. After relief of bilateral renal obstruction, there is an increase in delivery of sodium to the

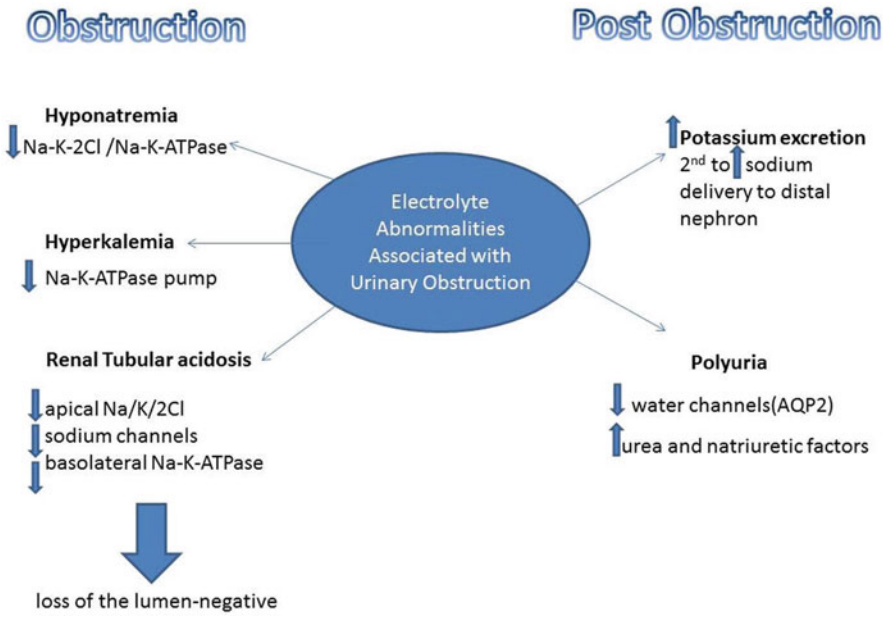

Fig. 15.1 Electrolyte abnormalities associated with obstruction and post obstruction

distal nephron resulting in net and fractional excretion of potassium. Patients can also develop the polyuria phase of recovery due to decrease expression of water channels (AQP2) and accumulation of electrolytes, urea, and natriuretic factors that occur while the obstruction is present.

Case # 1 Follow-Up and Discussion

The patient presented with newly diagnosed lymphoma as seen in the CT scan shows the presence of significant mass with bilateral moderate hydronephrosis. The patient maintained good urine output (75–100 ml/h urine output) throughout, and received intense prophylaxis against tumor lysis syndrome while immediately receiving Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine and Prednisone (R-CHOP) with significant improvement of his abdominal mass. He had notable improvement in his renal function and follow-up ultrasound indicated resolution of the hydronephrosis. His tumor regressed in a span of 5 days and he was able to be discharged with creatinine of 1.5 mg/dl. Hence, the most appropriate answer is d. Alternatively, had the rate of urine output been low, and given the high risk for tumor lysis syndrome and the risk of worsening renal function, a temporary nephrostomy could be justified.

Clinical Presentation

Presentation of UTO can vary with no symptoms to pain and hematuria depending on the type and duration of obstruction. For example, patients with chronic hydronephrosis may be completely asymptomatic with incidental finding of a rise in serum creatinine. On the other hand, patients with acute obstruction due to kidney stones or bladder cancers may have pain, dysuria, and hematuria. Anuria or even oliguria may not be present unless the obstruction is complete. Therefore, "a good urine output" does not exclude urinary obstruction. An inexpensive and least invasive investigation that can virtually rule out an obstruction is a careful ultrasonic examination of the kidney ureters and bladder, especially if a repeat one after 12–24 h is found to be normal. Bilateral urinary obstruction often results in decreased urinary output while unilateral obstruction would not.

Diagnosis

Initially, a detailed history concerning pain, acuity of symptoms, urinary complaints, infections, and hematuria combined with a physical exam can provide significant information about the cause of the rise in creatinine. Imaging will further confirm any suspicion of obstruction. The different imaging modalities, commonly used to diagnose UTO, are ultrasound, CT, nuclear medicine, and magnetic resonance imaging (MRI).

Non-dilated obstructive uropathy is not a common phenomenon in the general population (4 %); however, in the cancer population there is an increased incidence and approximately 60 % are associated with an intrapelvic malignancy. When a patient with renal failure presents with the associated findings of an intrapelvic or retroperitoneal tumor, it is imperative that obstructive uropathy be ruled out, even in the absence of dilatation [10, 11]. Ultrasound is usually the first choice due to its availability, and no exposure to radiation (Fig. 15.2). The false-positive rate (nonobstructive hydronephrosis) is between 10 and 20 % and is not as effective in determining the etiology and location of obstruction. A retrograde pyelogram or an antegrade pyelogram may be a better modality when all other etiologies of renal failure are ruled out. A possible mechanism of nondilatation of the UTO is encasement of the ureters in tumor or fibrous tissue, abnormal ureteral peristalsis, urinary debris, and ureteral edema.

Regardless of the actual mechanism, MRI may be an alternative to CT if indicated. Percutaneous nephrostomy (PCN) and antegrade urography are utilized after ureteral obstruction is detected in order to relieve the obstruction, and may be done to establish a diagnosis of obstruction among patients who are at very high risk for obstruction and who have a nondiagnostic CT or ultrasound [12]. While some centers use nuclear medicine scan, they are not standard of care to diagnose urinary obstruction since the diagnosis can simply be made with an ultrasound in majority of the cases. In addition, nuclear scans are less useful when renal function is diminished because of delayed isotope excretion and diuretic resistance.

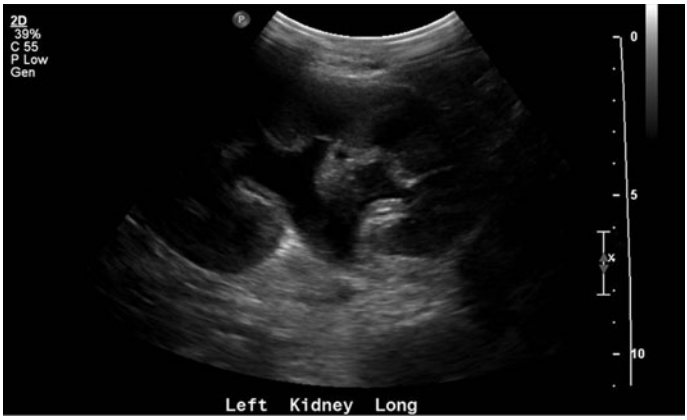

Fig. 15.2 Ultrasound showing hydronephrosis in a stem cell transplant patient with BK virus. Significantly dilated pelvicalyceal system is demonstrated

Case #2
A 22-year-old female with a past medical history of relapsed acute lymphocytic leukemia (ALL), status: post-haploidentical stem cell transplant 2 months ago complicated with history of fevers and fungal pneumonia. She is admitted with gross hematuria and clots. Her renal function worsened from 0.6 to 2.6 mg/dl (23.0 ml/min/1.73 m^2 GFR). Her blood pressure was 110/80 mmHg and HR 100 beats/min. Physical exam was essentially negative except for mild crackles on lung exam bilaterally. Her serum potassium was 5.0 mEq/L, bicarbonate 15 mEq/L, and urine analysis revealed > 100 RBC with gross hematuria.

What is the most likely cause of this patient's hematuria and obstructive AKI?

a. CMV nephritis
b. BK nephritis
c. Acute tubular necrosis
d. Radiation nephropathy

Treatment

In cancer patients, decompressing the urinary tract is crucial to prevent chronic damage to kidney. Once a decision is made to decompress the obstruction, it is preferable to do that at the earliest convenience. However, an emergency decompression may not be necessary especially over the weekend or in the after-hours if the kidney function, serum electrolytes, and patient's clinical conditions such as volume status are

stable. However, it is important to balance patient quality of life, need for long-term renal preservation and risk of complication should be taken into account in the setting of a poor prognosis or very short life-expectancy. Treatment of UTO usually aims to eliminate the obstruction by surgery, instrumentation (e.g., endoscopy, lithotripsy), or drug therapy (e.g., hormonal therapy for prostate cancer). Since, surgery is not possible in all cases, nephrostomy or ureterostomy can help to decompress the urinary tract. PCN is currently the preferred supravesical diversion because of its minimal morbidity and mortality [13]. A ureteral stent or PCN usually becomes permanent in patients with advanced cancers because they are not curable [14].

UTO in cancer patients due to tumor involvement can be alleviated by introducing indwelling Foley's catheters, PCN, ureteral stents in conjunction with undergoing treatments for the underlying malignancy to help reduce the tumor burden and hopefully resolve the obstruction.

Some of the other etiologies of UTO in the cancer population are retroperitoneal fibrosis (Ormond's disease), which is characterized by the presence of inflammatory and fibrous retroperitoneal tissue that often encases the ureters or abdominal organs [15]. It is described as idiopathic or secondary in nature. Secondary causes that are relevant to our cancer population are as follows :

Malignancy: carcinoid, Hodgkin's and non-Hodgkin's lymphoma, amyloid, sarcomas, colorectal, breast, prostate, and bladder carcinoma

Surgery: retroperitoneal in location such as: lymphadenectomy, colectomy, aortic aneurysmectomy

Radiation therapy: testicular seminoma, colon, pancreatic cancer.

Drugs: ergot-derivatives, methysergide, bromocriptine, beta blockers, methyldopa, hydralazine, analgesics.

Infections: tuberculosis, histoplasmosis, actinomycosis.

Retroperitoneal hemorrhage

Treatment due to secondary retroperitoneal fibrosis is focused on treatment of the underlying disease. Steroids have been used to help alleviate the inflammatory component that is driving the fibrosis. Relieving the obstruction with PCN and stents have been used if symptoms are severe while disease is treated. Untreated patients may develop severe complications or progress to end-stage kidney disease [15].

Treatment modalities of BK-associated UTO in HSCT population are limited due to no effective treatment for BK infection. Interventions listed below in setting of UTO are temporary symptom and obstruction relief in BK-related UTO in HSCT patients.

1. Intravenous fluid hydration and continuous bladder irrigation: maintaining high platelet counts, appropriate red cell counts and levels of clotting factors, pain relief, clot extraction and continuous bladder irrigation with normal saline for prevention of clots, and bladder tamponade [16].
2. Hyperbaric oxygen (HBO used in BK cystitis): in a recent study of 16 patients with BK cystitis, 15 patients (94 %) showed complete resolution of hematuria and decreased BK viruria. HBO can stimulate fibroblast proliferation, angiogenesis, and wound healing; however, it does not directly treat BK virus associated infection [17].

3. Nephrostomy tube placement: BKV-related ureteral stenosis in kidney transplant patients has been reported to be at 2–6 % [18]. It has been shown that BKV was harbored in ulcerated, stenosed ureters. In HSCT there has been reports of reversible stenosis and need for nephrostomy tube placement with improved outcomes [2].

In a retrospective study in 2007 of 102 patients who underwent decompression for malignant ureteral obstruction from 1991 to 2003, 68 % of patients had bilateral obstruction. PCN or ureteral stent was successful in 95 % of cases. Fifty-three percent of patients developed complications such as urinary tract infection. A multivariate analysis revealed independent prognostic factors for inferior overall survival were presence of metastases (P-Value 0.020) and diagnosis of malignant urinary obstruction in previously established malignancy (P value 0.039; median survival was 7 months) [19].

Case #2 Follow-Up and Discussion
The patient likely has BK nephritis following HSCT. She underwent continuous bladder irrigation for several weeks. However, due to her significant hydronephrosis (Fig. 15.2), she required bilateral nephrostomy tube placements (PCN) with improvement of her creatinine to baseline of 1.0 mg/dl. In the following months, she continued to have multiple episodes of PCN malfunction and infections. Her creatinine continued to rise in the last year with creatinine baseline at 3.5 mg/dl with estimated GFR 15 cc/min. Due to her severe history of BK cystitis she developed a severely scarred bladder that was no longer functional. She continued to have PCN until she developed uremia and irreversible renal failure. From her ALL standpoint she remains cancer free; however, she is on dialysis.

Summary

With the advances in cancer therapy and the prolongation of life it is imperative for other specialties to evolve to help improve the quality of life of the cancer patient and overall health. Onconephrology has emerged with the focus to advance and maintain kidney health in the cancer population. In this chapter, we have illustrated the different etiologies, presentations, and treatments of UTO. Although a simple and easily reversible cause of renal failure in the general population, it is more challenging in the cancer population. Understanding that further cancer treatment are contingent on normal renal function, makes obstructive uropathy to be an easily reversible cause of renal failure that should be high on the differential for renal failure.

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Chapter 16
Cancer in the Kidney Transplant Recipient

Sharad Sathyan, Madhu Bhaskaran and Vinay Nair

List of Abbreviations

ACKD	Acquired cystic kidney disease
AJCC	American Joint Committee on Cancer
AK	Actinic keratosis
BCC	Basal cell cancer
BM	Bone marrow
CNI	Calcineurin inhibitors
CNS	Central nervous system
EAR	Excess absolute risk
ED&C	Electrodessication with curettage
EGFR	Epidermal growth factor receptor
ESKD	End stage kidney disease
GPCR	G protein cellular receptor
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
KDIGO	Kidney disease improving global outcomes
KS	Kaposi's sarcoma
LCDD	Light chain deposition disease

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LMP	Latent membrane protein
MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
mTOR	Mammalian target of rapamycin
PET	Positron emission tomography
PTLD	Posttransplant lymphoproliferative disorder
SCC	Squamous cell cancer
SIR	Standardized incidence ratio
SRTR	Scientific registry of transplant recipients
TGF	Transforming growth factor
UV	Ultra violet
VEGF	Vascular endothelial growth factor
XRT	Radiation therapy

Renal transplantation dramatically improves survival and quality of life in patients with end-stage kidney disease (ESKD) [1, 2]. As these patients live longer on immunosuppression they have been found to develop a number of immunosuppression related complications including cardiovascular disease, infection, and malignancy. In fact malignancy is the third most common cause of mortality posttransplantation [3, 4]. With recent advancements in kidney transplantation, the rates of rejection have decreased and those of survival have increased [5, 6]. Longer patient and graft survival, and associated exposure to immunosuppressants, have resulted in higher rates of malignancy in these patients. In addition, today's transplant candidates are often elderly and are more likely to present with a history of cancer. Such patients require special consideration when determining whether they are transplant candidates and how long after the treatment of cancer should they be offered transplantation. As candidates have aged, so have kidney donors. The utilization of expanded criteria donors, largely determined by age, has risen in recent years due to the current organ shortage. As a consequence, a potential donor may have had a prior malignancy or be at risk of harboring a malignancy at the time of donation which could be transmitted to the recipient. Better understanding of the complex interplay of these factors requires an understanding of the epidemiology and pathogenesis of posttransplant malignancy. In addition, understanding which malignancies are at the highest risk of transmission and recurrence is of paramount importance when educating ESKD patients both before and after kidney transplantation.

Epidemiology

Case #1
A 62-year-old Caucasian female with ESKD secondary to diabetes comes to your office for a transplant evaluation. She has been on hemodialysis for 6

months and is eager to receive a kidney transplant. She is very worried about the risk of malignancy posttransplantation, and asks you how a kidney transplant impacts her risk for cancer. Your best answer is:

a. There is no increased risk of cancer after the kidney transplant.
b. There is no increased risk of cancer as long as she has age appropriate cancer screening.
c. There is an increased risk of cancer after transplantation compared to the general population but not the ESKD population.
d. There is an increased risk of cancer after transplantation compared to both the general and ESKD population.

In a large study of all solid organ transplants utilizing data from the scientific registry of transplant recipients (SRTR) from nearly 21 years of follow-up, the authors identified 10,656 cases of malignancies, resulting in an incidence of 1375 per 100,000 person years [7]. The risk of malignancy in the transplant population compared to the general population is expressed as standardized incidence ratio (SIR) and excess absolute risk (EAR) [7, 8]. The SIR is calculated by dividing the observed cases of malignancy by the expected cases of malignancy. The EAR is calculated by subtracting the expected incidence of malignancy from the observed incidence of malignancy. Transplant recipients have an SIR of 2.1 and an EAR of 719 per 100,000 person years for malignancy. While the age and the time to presentation varies with different cancers, the mean age at presentation is in the fifth decade of life and the time to presentation is 3–5 years posttransplantation [9]. Although certain cancers such as renal cell carcinoma (RCC) are found at a higher prevalence in ESKD patients, the overall incidence of cancer is significantly higher in transplant patients [8].

Case #1 Follow-Up and Discussion

The correct answer is choice d. Although studies have shown that certain cancers are more likely to occur in patients with chronic kidney disease or with ESKD, the overall incidence of cancer clearly increases further after kidney transplantation.

After kidney transplantation most cancers have an elevated SIR. Liver cancer occurs mainly in liver transplant patients and kidney transplant patients with chronic hepatitis. The SIR for lung cancer is higher in kidney transplant patients, but only marginally (SIR 1.46). Lung cancer tends to be seen as much more common in lung transplant and heart transplant patients. The reason is thought to be related to greater incidence of smoking in these patients and perhaps a higher degree of immunosuppression. Kidney cancer is seen at a much higher SIR in kidney transplant recipients, and this is secondary to the elevated risk of malignancy associated with acquired cystic kidney disease (ACKD).

The cancers with the highest SIR after transplantation include non-Hodgkin lymphoma, Kaposi's sarcoma (KS), nonmelanoma skin cancer, and cancer of the lip. In all solid organ transplants, liver cancer also has a very high SIR, but again this is mainly due to a high incidence of liver cancer in liver transplant patients. Cancers with elevated risk posttransplantation are listed in Table 16.1, in order from highest to lowest incidence with their associated SIR [7]. Incidence and SIR used for Table 16.1 is based on publication by Engels et al. [7].

The four most common cancers seen in the transplant patients are cancer of the lung, liver, kidney, and non-Hodgkin lymphoma. [7] Although cancers such as KS have a much higher SIR posttransplant, they are still rare compared to other more common tumors.

Etiology and Pathogenesis

Case #2
Which of the following have not been implicated in the increased risk of malignancy after kidney transplantation?

a. Impaired defense against viruses
b. Impaired immune surveillance against tumor cells
c. Inhibition of the mTOR pathway
d. Upregulation of transforming growth factor beta (TGF-β)

The etiology of cancer posttransplantation is multifactorial. It involves a combination of impaired defense mechanism against viruses, impaired immune surveillance against tumor cells, DNA damage or interference with DNA repair by the immunosuppressive agents, exposure to carcinogenic agents like ultra violet (UV) light, genetic predisposition, and upregulation of cytokines such as TGF-β and vascular endothelial growth factor (VEGF) which may promote tumor progression. Cancers that are related to viral infections, such as non-Hodgkin's lymphoma, KS, etc. have a particularly increased risk of malignancy [9, 10].

The role of immunosuppressive agents in cancer following transplantation is highlighted by the fact that there is a two to fourfold higher incidence of cancer in patients with heart transplant compared to kidney transplant [11, 12]. This is presumed to be due to the higher level of immunosuppression needed. Similarly, patients who have had pretransplant immunosuppressive therapy have a higher incidence of cancer posttransplant compared to those who have not. Immunosuppressive agents may predispose to malignancy from impairing the ability to eliminate tumor cells. In experimental and animal models, the role of T lymphocytes, natural killer (NK) cells, and cytokines in protection of the host from tumors has been demonstrated [13]. Immunosuppressive agents like azathioprine and cyclosporine sensitize DNA to UV light and predispose to mutations and skin cancers. They can impair DNA

Table 16.1 Cancers with elevated risk after transplantation

Cancer type	SIR	Observed incidence/100,000 person-years
Non-Hodgkin lymphoma	7.54	194
Lung	1.97	173
Liver	11.56	120
Kidney	4.65	97
Colorectum	1.24	80.9
Melanoma	2.38	49.2
Thyroid	2.95	30.7
Urinary bladder	1.52	29
Poorly specified histology	2.11	26.6
Nonmelanoma skin	13.85	23.7
Pancreas	1.46	20.3
Stomach	1.67	19.6
Oral cavity and pharynx	2.56	19.2
Lip	16.78	16.8
Kaposi's sarcoma	61.46	15.5
Plasma cell neoplasms	1.84	15.2
Oropharynx	2.01	13.7
Acute myeloid leukemia	3.01	13.2
Larynx	1.59	12.5
Esophagus	1.56	12.4
Anus	5.84	11.6
Hodgkin lymphoma	3.58	11
Soft tissue including heart	2.25	8.4
Vulva	7.6	7.5
Salivary gland	4.55	7.2
Small intestine	2.43	6.5
Testis	1.96	5.2
Intrahepatic bile duct	5.76	4.9
Chronic myeloid leukemia	3.47	4.9
Gallbladder	2	2.8
Penis	4.13	2.8
Eye and orbit	2.78	2.7
Acute lymphocytic leukemia	2.06	2.2

repair mechanisms and apoptosis, while at the same time enhancing angiogenesis and tumor growth [14, 15]. In addition, they have been shown to promote clonal proliferation of cells with p53 gene mutations resulting in skin malignancies [16]. Immunosuppressants may also act by impairing antiviral activity, predisposing to infection with oncogenic viruses, and eventual malignant transformation. It has been noted that patients who are naïve to viruses like Epstein–Barr virus (EBV) and human herpes virus (HHV) are more likely to develop malignancies posttransplantation and reduction or withdrawal of immunosuppression often results in regression of the malignancy [17, 18]. These virus associated tumors may be more responsive to reduction in immunosuppression, presumably due to increased recognition of nonself through presentation of viral peptides, compared to chemical and environmental carcinogens [19]. Cytokines such as IL-6, IL-10, and latent membrane protein-1 (LMP-1) have also been implicated in tumor genesis. IL-6 acts as an autocrine and paracrine growth factor. Its production is known to be enhanced by cyclosporine and OKT3. IL-10 prevents antigen presentation, interferes with antitumor cytokine production and cytotoxic T lymphocyte response, and prevents programmed cell death. IL-10 transcripts have been seen in squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) lesions. High-production genotype of IL-10 has been found to be more frequent in these malignancies. Posttransplant lymphoma or posttransplant lymphoproliferative disease (PTLD), is often related to EBV viral infection of B cells. In such cases, IL-10 production is induced by viral LMP-1 gene, and serves as an autocrine growth pathway. Other factors involved in tumor genesis include VEGF and TGF-β. VEGF is critical in angiogenesis, and necessary for tumor growth, progression, invasion, and metastasis [20]. Dysregulation of TGF-β is known to promote tumor genesis. TGF-β can also promote angiogenesis and lead to metastasis [21]. Cyclosporine is known to induce IL-6 and TGF-β production. Tacrolimus has also been shown to promote TGF-β production [22].

Last, the chronic inflammation and activation of the immune system due to the alloreactivity or viral infection can predispose to tumor genesis. Mechanisms include infiltration with T regulatory cells, immature dendritic cells, expression of negative costimulatory pathways, and production of tumor growth factors [19].

On the contrary, mammalian target of rapamycin (mTOR) inhibitors have been used to treat cancer, and may have a protective effect in transplantation. Rapamycin has been shown to block the growth of tumors, and this has been consistently shown in several clinical studies [23]. Mechanisms include, its ability to reduce TGF-β production [23] and inhibit IL-10 production [24–29].

Case #2: Follow-Up and Discussion

The correct answer is choice c. Option a, b, and d are all potential mechanisms of posttransplant carcinogenesis. As mentioned above, mTOR inhibitors reduce cancer risk in transplant patients and have been used to treat certain malignancies.

Case #3
A 48-year-old West Indian male who received a kidney transplant 10 months ago presents to your office with a rash. He has a history of hypertension, hyperlipidemia, and ESKD was secondary to diabetes. Over the past few weeks he developed reddish brown, slightly raised nodules on the feet and arms. He has had excellent graft function and has been compliant with his medications. His immunosuppressive agents include tacrolimus, mycophenolate mofetil, and prednisone. He also reports mild lower extremity edema. He denies fevers, and the lesions do not bleed. You review his labs and find that he has no protein in the urine. His review of systems is otherwise negative. Your diagnosis is:
a. Drug rash
b. An angioproliferative disorder due to HHV-8 infection
c. Bacillary angiomatosis
d. Syphilis

Kaposi's Sarcoma

KS is an angioproliferative disorder, caused by HHV-8. The SIR for this cancer is more than 60, and has one of the greatest increases in incidence compared to all other cancers in transplant patients [7]. KS is three times more likely to occur in transplanted men than women. It is more common in patients of Jewish, Mediterranean, Caribbean, and African origins, and the affected patients are usually in their 40s. This disease is believed to be caused by an infection of the endothelium with HHV-8 [30, 31]. The incidence of KS has been found to be higher among those with preexisting anti-HHV antibodies [32]. Other risk factors for developing KS include the use of calcineurin inhibitors (CNI), induction therapy with rabbit anti-thymocyte globulin, multiple sexual partners, and genetic predisposition [33].

HHV-8 can have a transformative effect on endothelial cells. Most of the cells within the KS lesions reveal latent infection with HHV-8, while a small proportion of cells express lytic cycle genes. Transition to the lytic phase is mediated by several cytokines and growth factors. During the lytic phase, the production of viral gene products leads to replication. The viral genome also harbors several oncogenes which interfere with apoptosis and cell cycle regulation, leading to tumor genesis. There is a noted increase in G protein cellular receptor (GPCR) expression, which causes the cell to enter the replicative stage [36]. Other chemokines and growth factors, such as IL-6, IL-8, CXCR 3,4, and CCR1,5 are implicated in angiogenesis and cell migration [33–36]. HHV-8 encodes K3 and K5 membrane proteins which downregulate major histocompatibility complex (MHC) antigen presentation and help the virus evade the hosts cytotoxic response [37].

Skin involvement is the most common manifestation of KS. It usually appears as red to purple maculopapular or nodular cutaneous lesions. Patients with KS may have lower extremity lymphedema due to dermal lymphatic involvement or dermal infiltration. KS can also involve the viscera such as the gastrointestinal tract, lungs, and lymphoid tissue. Pleural or pulmonary involvement is seen in advanced stages of the disease [33]. Isolated visceral involvement occurs in around 10 % of cases, and portends a poor prognosis [30].

KS is also clinically staged as follows:

Stage 1: Involvement of a single limb with localized skin lesions.
Stage 2: Involvement of > 1 limb with skin lesions.
Stage 3: Involvement of one or more viscera or lymph nodes.
Stage 4: Presence of a life-threatening infection or other neoplasia in association with any of the stages noted above.

Case #3 Follow-Up and Discussion
The reddish brown, slightly raised nodules on the feet and arms suggests HHV-8 related disease. His rapid plasma reagin (RPR) was negative and he had no other signs of drug induced disease. HHV-8 PCR was positive and immunosuppressive therapy was reduced. Correct answer is b.

The most prudent step in treating KS is to reduce the immunosuppressive therapy to the lowest possible level while maintaining allograft function. This reduction in immunosuppressive therapy restores the anti-HHV T cell response and can lead to resolution of the KS lesions [38]. One strategy which has been very successful is switching to sirolimus-based immunosuppressive regimen. In an Italian study of 15 patients with KS, clinical and histological resolution of skin lesions, while preserving graft function, was achieved by changing immunosuppression to Mammalian target of rapamycin inhibitor-based therapy [39]. Mammalian target of rapamycin inhibitors impair VEGF production, and limit angiogenesis and tumor progression. Additionally, it has been shown that genesis of KS involves stimulation of tuberin phosphorylation by vGPCR and activation of mTOR. This suggests a role for mTOR inhibitors in preventing sarcoma genesis [40, 41].

Localized therapy such has radiation, laser, surgical excision, and topical antivirals have been occasionally reported to be successful [33, 42, 43]. In some cases of KS with visceral involvement, systemic chemotherapy may be required [44]. This is particularly true in patients that have failed to respond to reduction in immunosuppression alone. Paclitaxel and docetaxel have been used successfully, and other agents like pegylated liposomal doxorubicin, vinca-alkaloids, etoposide, gemcitabine, bleomycin, interferon α-2, and thalidomide have also been used [43, 45]. The studies are diverse, lack consistency, and the overall evidence does not allow a recommendation for a specific chemotherapy.

Case #4
A 50-year-old Caucasian male presents for his annual transplant follow-up. He received a deceased donor kidney transplant 9 years ago. Apart from an early cellular rejection he has done well and is compliant with his medications. He has enjoyed excellent allograft function. On exam, you find two raised brown keratotic lesions on his left forearm. You become suspicious and send him for a skin biopsy. The skin biopsy is most likely to show:

a. Dysplastic keratinocytes involving the full thickness of the epidermis with some evidence of keratinization.
b. Proliferation of atypical basaloid cells that form an axis parallel to the epidermal surface and cleft like spaces containing alacian blue positive material.
c. Neoplastic melanocytes.
d. Cluster of small blue cells.

Skin Cancers

Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) account for more than 90 % of all nonmelanoma skin cancers in transplant patients. Cancer registries are not required to report these tumors, but their incidence is known to be significantly increased after solid organ transplantation. Skin cancers are known to develop in more than 50 % of all recipients and account for up to 40 % of all malignancies post-solid organ transplantation [46, 47]. The incidence of SCC can be increased 65–250 times compared to the general population, while that of BCC is increased ten times [48]. These cancers appear to be age dependent and occur sooner in older patients following transplantation [46, 47]. Proposed risk factors for posttransplant skin cancer include geography (Australia has the highest incidence) [49], UV light exposure, and pre- and posttransplant history of actinic keratosis (AK), SCC, or BCC [50, 51]. The risk of nonmelanoma skin cancer has been found to be greater in heart, lung, and combined kidney and pancreas transplants when compared to kidney or liver transplants alone [52]. This may be related to a greater intensity of immunosuppression in specific types of organ transplants [53]. Other risk factors include polymorphisms in the folate pathway [54], and infection with human papilloma virus (HPV) [55].

Direct carcinogenic effects of agents like UV light exposure and immunosuppressants, such as cyclosporine, tacrolimus, and azathioprine, along with impaired tumor surveillance facilitate development of skin cancers. Oncogenic viruses like HPV may impair DNA repair mechanisms while proliferating themselves, and can augment the oncogenic response [56].

The kidney disease improving global outcomes (KDIGO) guidelines recommend that transplant patients have annual skin and lip cancer screening performed by

a qualified physician [57]. UV exposure is a major risk factor for development of nonmelanoma-based skin cancers, and the use of sunscreen has been found to reduce the incidence of skin cancer in transplant recipients [58]. Reduction in immunosuppression and use of agents such as the mTOR inhibitor Rapamycin has also been somewhat effective in reducing the incidence and mitigating the aggressiveness of skin cancers [59–61]. Similarly systemic retinoids, like acitretin, have been shown to reduce the incidence of AK and SCC [62].

Below we discuss treatments for the common skin cancers seen in transplant patients.

Actinic Keratosis

This is a precursor lesion to SCC which warrants aggressive management. Standard modalities include cryotherapy and electrodessication with curettage (ED&C). Other options include topical 5-fluorouracil (5-FU) and topical immunomodulators like imiquimod [46, 63]. These treatments can be cycled for maximum efficacy. Another new treatment option is photodynamic therapy. This involves the topical application of a photosensitizer such as aminolevulinate (ALA) or methyl-aminolevulinate (MAL) to affected skin area, followed by irradiation with visible light. This technique selectively destroys cells in the sensitized target area [64].

Squamous Cell Carcinoma

Before determining the treatment course, SCC should be classified into low risk or high risk. The clinical and pathological features of high risk include: [65]

1. Size: > 0.6 cm, face (excluding cheeks and forehead)

   > 1 cm, cheeks, forehead, neck, and scalp
   > 2 cm, trunk and extremities
2. Multiple SCC
3. Recurrence
4. Rapid growth
5. Indistinct borders
6. Ulceration
7. Presence of satellite lesions
8. High-risk location: central face, lips, over parotid glands, ear, temple, scalp, digits, and genitalia
9. Histology: Poor differentiation; Deep extension of tumor into subcutaneous fat-Clark$>$ IV, lesion thickness > 4 mm; perineural, perivascular, or intravascular invasion

Low-risk SCC can be managed with Mohs micrographic surgery or traditional surgical excision. Mohs procedure is particularly beneficial when tissue conservation is necessary. Another modality is ED&C, which is useful in the presence of multiple low-risk lesions. On the other hand, high-risk SCC necessitates early and aggressive resection. Mohs micrographic surgery is the treatment of choice for low-risk SCC, and it allows for evaluation of all the margins of the excised tissue. This is combined with reduction or modulation in immunosuppression with the introduction of an mTOR inhibitor such as sirolimus [46, 59, 61, 66, 67].

The presence of nodal involvement, perineural involvement, or incomplete excision with positive margins is an indication for adjuvant radiation therapy (XRT) [68]. Treatment of metastatic SCC is challenging, and platinum-based chemotherapeutic agents and capecitabine, an oral prodrug of 5-FU, have been used. New drugs targeting other pathways in the treatment of advanced SCC including epidermal growth factor receptor inhibitor (EGFR) are being evaluated [46, 69, 70].

Basal Cell Carcinoma

Management is similar to that in immunocompetent patients. BCC is less aggressive and has less morbidity and mortality when compared to SCC. Prognosis is usually good, and metastatic disease is rare. For superficial low-risk BCCs, treatment with excision, ED&C, topical 5-FU or imiquimod, cryotherapy, and photodynamic therapy can be used [71–73].

Features of high risk of recurrence include: [65]

1. Location and size: Greater than or equal to 6 mm in diameter in high-risk areas (e.g., central face, nose, lips, eyelids eyebrows, periorbital skin, chin, mandible, ears, preauricular and postauricular areas, temples, hands, feet)
2. Over 10 mm in diameter in other areas of the head and neck
3. Over 20 mm in diameter in all other areas (excluding hands and feet)
4. Aggressive pathological features- Morpheaform, sclerosing, or mixed infiltrative, micronodular, basosquamous (keratinizing)
5. Recurrent lesions
6. Lesions in sites of prior radiation therapy
7. Lesions with poorly defined borders
8. Lesions in immunocompromised patients
9. Perineural invasion

Treatment options include Mohs surgery (preferred procedure), surgical excision with postoperative margin assessment, and radiation therapy; particularly in elderly or those who cannot tolerate surgery. For metastatic disease, platinum-based chemotherapeutic agents, cetuximab, and more recently vismodegib, an oral inhibitor of the hedgehog signaling pathway, have been used [74–76].

Melanoma

Melanomas have a 3.6-fold elevated risk incidence in the transplant population [77]. Risk factors include the use of antilymphocyte antibody agents, fair skin, presence of freckles, and light hair and eyes [78]. According to one study, risk of melanoma for African Americans may be particularly higher, and it increased up to 17-fold compared to the general population [77]. Melanomas in the posttransplant population may be multiple, and the mean age to diagnosis is 5 years after transplantation. More than a third of all patients with melanoma after transplantation have other malignancies. Melanoma can also be transmitted from an organ donor [47, 79].

Nevi at higher risk for melanoma can be identified by: asymmetry, border irregularities, color variation (brown, red, black or blue/gray, and white), diameter ≥ 6 mm, and evolving (ABCDE). The ugly duckling sign reveals a nevus looking different from surrounding lesions [80, 81]. The finding of such lesions warrants a prompt referral to a dermatologist, followed by an excision biopsy including 2 mm of normal skin and a cuff of the subcutaneous fat [82].

Prognosis is determined by the thickness of the lesion, ulceration, and mitotic rate of which thickness is the most important. The American Joint Committee on Cancer (AJCC) has developed a staging system which can be used to estimate the survival rates [83]. Malignant melanoma cause-specific patient survival is similar to transplant naïve patients except for those with a Breslow thickness between 1.51–3 mm or a Clark level of III or IV [83, 84]. Another report also revealed inferior patient survival in transplant patients with a Breslow thickness of > 2 mm [85]. Treatment includes wide surgical excision and a careful reduction in immunosuppression. In an animal model changing immunosuppression from a CNI to mTOR-based therapy was found to be beneficial; however, this strategy has not been confirmed in humans [23]. Patients with melanomas that have a high risk of dissemination (stage IIb, IIc) or lymph node involvement (stage III) have been shown to benefit from adjuvant immunotherapy with interferon-α [86]. However, the benefit of interferon-α in transplant patients with melanoma must be carefully balanced with the risk of triggering rejection in kidney transplant recipients. Other new immunotherapies are being developed, which may have better tolerability in transplant patients. Unfortunately, recurrence is frequent, occasionally as late as 10 years after the initial treatment [23, 47].

Merkel Cell Carcinoma

Merkel cell carcinoma is an aggressive neuroendocrine tumor of the skin. It usually affects the head, neck, and upper extremity. Mean time to diagnosis is 7 years posttransplant, and age of onset is younger in the transplant population [47, 87]. Development of Merkel cell carcinoma may be linked to an infection with the Merkel cell polyoma virus. [88] This disease carries a poor prognosis with a > 50 % mortality after 2 years. Treatment options include Mohs' surgery or wide surgical excision

with a sentinel lymph node biopsy. Lymph node metastases are frequent and usually warrant lymphadenectomy with radiation and systemic chemotherapy [47].

Case #4 Follow-Up and Discussion
This patient most likely has SCC of the skin, Choice a. The second choice is BCC, the third choice is melanoma, and the fourth option is Merkel cell carcinoma. As discussed above, the most common skin cancers in renal transplant patients are SCC.

Case #5
A 48-year-old Asian female comes to your office for her annual visit. She had received a deceased donor kidney transplant 6 years ago. She is compliant with all her medications and has had excellent graft function. She reports no major complaints, except for occasional rectal bleeding and a feeling of "something being there." On examination, you palpate a mass in the anorectal region. You are concerned that she may have a cancer. You tell her that this cancer is most likely due to:
a. Infection with HHV-8
b. Infection with HPV
c. Infection with human immunodeficiency virus (HIV)
d. Chronic constipation

Anogenital Cancers

The risk for cancers of the anogenital region is increased almost 100-fold in the posttransplant period and can account for 2–3 % of all malignancies posttransplant. These include cancers of the anus, vulva, vagina, cervix, penis, and scrotum. They are more frequent in women (2:1) and tend to occur late posttransplant [89]. They are strongly associated with HPV infection, particularly the high-risk subtypes (16 and 18) [90]. Other risk factors include HIV, cigarette smoking, prior HPV related anogenital malignancy, and history of infection with genital herpes. The median age at presentation is in the fifth decade, and they tend to be multiple extensive maculopapular lesions. They may resemble genital warts and can be localized or invasive [89]. For local noninvasive lesions, treatment options include topical fluorouracil, laser, electrocautery, topical imiquimod along with reduction in immunosuppression. For invasive tumors, treatment involves wide excision, lymphadenectomy, and adjuvant chemo and/or radiation therapy [91]. Screening strategies, such as annual

gynecological exams including a cervical smear, have been shown to be beneficial and cost effective posttransplantation. Similarly, anal cytology and high-resolution anoscopy may be beneficial in select patients [92–94]. The HPV vaccines are recommended in the female transplant population between the ages of 9–26, although the immune response is not clearly delineated [95].

Case #5 Follow-Up and Discussion
The correct answer is answer choice b. Anogenital cancers are strongly associated with HPV infection of the subtype 16 and 18.

Renal Cell Carcinoma

RCC has a somewhat unique relationship to ESKD and transplantation, as there is not only an increased risk associated with ESKD and transplantation but it can also be a cause of ESKD [7, 8]. When compared to the general population, the SIR of RCC is significantly greater in kidney transplant recipients. However, it is very similar to patients with chronic kidney disease and those on dialysis [7, 8]. RCC is more common in the native kidneys than in the transplanted kidneys. RRC can also rarely be transmitted from the donor kidney. The increased risk of RCC is believed to be due to acquired cystic kidney disease (ACKD), and this is borne out by the fact that the SIR is maximally increased after kidney transplant compared to other organ transplants [7, 96, 98]. Indeed, after lung transplant there is no notable increase in SIR for RCC, and the increase after lung and liver transplant is small [7].

The presence of ACKD is associated with dialysis vintage [99]. Posttransplant RCC is usually incidental in nature. An ultrasound or a computed tomography (CT) scan may reveal a complex cyst or mass. Once a mass is found, biopsies are generally not performed. Staging is completed with a CT scan and a chest X-ray. Screening for RCC after transplantation is controversial. Cytology is not reliable posttransplantation. It is challenging to use iodinated contrast with CT scans, due to its potential deleterious effects on renal function, and gadolinium-based magnetic resonance imaging (MRI) imaging imparts a risk of nephrogenic systemic fibrosis. Ultrasound has been shown in one French study to have good sensitivity and specificity in identifying RCC in the native kidneys posttransplant [100]. The authors recommended obtaining a baseline ultrasound at the time of transplant and repeat ultrasounds after every 3 years. Authors of a more recent German study recommend annual screening in kidney transplant patients regardless of ACKD. They went on to recommend further imaging with a combination of CT and ultrasound based on Bosniak scores. RCC was more likely to occur in patients with Bosniak category 2F or more, accounting for more than 58 % of all cases [97]. Despite these studies, there is no good data that mortality is reduced by screening transplant patients for RCC.

The American Society of Transplant Guidelines do not recommend routine screening [101]. However, patients with a higher risk for RCC and those with a longer than average life expectancy, may benefit. This includes young patients with known cystic renal disease, those with prior RCC, and those with a history of analgesic nephropathy or tuberous sclerosis. RCC arising from ACKD have a greater percentage of the papillary type histology although clear cell histology is the most prevalent, and is frequently bilateral in comparison to sporadic RCC [97].

Treatment depends on the extent of the disease and the comorbidities of the patient. Localized lesions are managed with radical nephrectomy. Five year survival in such patients is approximately 80 %. Treatment may be accompanied by changes in immunosuppression, such as conversion of a CNI to an mTOR inhibitor, reduction in CNI or antimetabolite. Tumors in the transplanted kidneys are difficult to treat, due to the fact that there is a need to preserve renal function. For small peripheral tumors (< 4 cm) nephron sparing surgeries such as partial nephrectomy, cryoablation, or radio frequency ablation may be possible. Metastatic disease has been reported, and prognosis is generally poor. Radical nephrectomy with immune therapy using IL-2 and interferon-α have been reported, but are fraught with danger of precipitating rejection. Drugs such as sunitinib, sorafenib, temsirolimus, and everolimus (an mTOR inhibitor) can be used in metastatic disease. The mTOR inhibitors are particularly attractive because of the immunosuppressive properties in addition to the antitumor effects. Choosing the option of no treatment is also a reasonable palliative option in this case, due to the dismal prognosis [102, 103]. A detailed chapter on medical and surgical treatment of RCC is discussed elsewhere in this book.

Bladder and Other Urinary Tract Malignancies

Bladder and other urinary tract malignancies, including bladder cancer, are increased after transplantation, particularly among patients with exposure to cyclophosphamide, aristolochic acid (Chinese herb), or with a history of analgesic nephropathy [102–104]. The presentation is most commonly painless hematuria. Other presenting features are dysuria, flank pain, and urinary obstruction. Diagnostic tests include imaging of the upper urinary tract with an ultrasound or CT scan, urine cytology, and cystoscopy [102]. Treatment depends on the TNM stage and is similar to transplant naïve patients. Superficial tumors can be managed with transurethral bladder resection. Invasive tumors require more aggressive surgical therapies, including radical cystectomy with creation of an ileal conduit or an ileal neobladder. It must be noted that many of these procedures are more complicated due to the proximity of the kidney transplant graft. Nephroureterectomy is beneficial to prevent recurrent disease, and may be useful in multifocal disease [102, 105]. For patients with a high risk of recurrence, intravesical Bacillus Calmette-Guerin (BCG) or mitomycin is used in the general population. BCG is usually not recommended in a transplant setting, as it is a live attenuated bacteria; however, it has been used with variable success [106]. For metastatic disease, methotrexate, vinblastine, adriamycin, and cisplatin (MVAC)

has been used. Other regimes used include cisplatin, methotrexate, vinblastine, or gemcitabine with cisplatin. Traditional immunosuppressive agents like tacrolimus and mycophenolate are usually reduced during chemotherapy [102, 107]. Our standard practice has been to stop the antimetabolite (either mycophenolate or azathioprine) during chemotherapy, although this approach requires careful monitoring for rejection.

In addition to the risk factors above, BK virus (BKV) has been examined as a potential risk factor for urinary tract malignancy. Case reports suggest an association between BKV infection and the development of renal and bladder cancers in renal transplant recipients [108]. In the tumor cells, it is sometimes possible to detect fragments of the BK viral genome that could alter the control mechanisms of the cell cycle and DNA repair. An oncogenic potential of BKV has been observed in vitro and in animal models [109]. In humans, however, the implication of BKV in tumor development is still unclear.

Colon Cancer

Colon cancer has an increased SIR after kidney transplantation [7]. Often the patients are younger (< 50 years of age), and therefore, do not have screening colonoscopies. Studies from Sweden had reported that in addition to an increased incidence of colorectal cancer, right sided cancers were more common than left sided cancers [110]. Colorectal cancer in the transplant population seems to have a lower mean age of diagnosis (58.7 vs. 72 years) and a reduced 5-year survival (30.7 vs. 63.5 %) [111]. The incidence ratio for transplant patients below 50 years of age compared to the general population of the same age is 3. Median survival is reported to be 2.3 years after diagnosis, with 68 % having metastasis [111]. Reasons for the aggressive course may be related to carcinogenic effects of the immunosuppressive agents. Other genetic factors, geographic factors, as well as premalignant conditions are also believed to have a role in the pathogenesis. Based on current screening guidelines early colon cancer may be missed. Therefore some experts recommend screening colonoscopies beginning 2 years post transplantation, particularly in patients with additional risk factors [111].

Other Solid Tumors

The incidence of other solid tumors that have a greater frequency after transplant can be seen in Table 16.1. Risk factors for solid tumors after transplantation are the same as those in non-transplant patients. Most solid tumors are present more frequently after transplantation [7, 8]. In general, screening and treatment guidelines should be the same as for non-transplant patients.

Posttransplant Lymphoproliferative Disorders

Case #6
A 70-year-old Caucasian male underwent deceased donor renal transplantation 2 years ago with thymoglobulin induction and maintenance with tacrolimus and mycophenolate mofetil. He is concerned about weight loss over the past 6 months with associated occasional fevers and daily night sweats. His lactate dehydrogenase (LDH) is elevated, and his abdominal imaging shows enlarged lymph nodes. A diagnosis of lymphoma is eventually confirmed. The tissue specimen confirms the presence of CD20 positive B cells that stain positive for EBV. What is the best treatment option?

a. Rituximab alone
b. Reduction in immunosuppression alone
c. Reduction in immunosuppression combined with early rituximab
d. Chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone)

Post transplant lymphoproliferative disease (PTLD) is a significant complication of solid organ transplantation. It includes a spectrum of manifestations, ranging from a benign self limited form to a widely disseminated form [112]. The incidence is particularly high after heart, lung, intestinal, and multiorgan transplant (20–25 %), and is lower following kidney and liver transplantation (1–2 %) [12, 113]. The increase in risk is up to 120 % higher when compared to the general population. Non-Hodgkin's lymphoma accounts for 70 %, multiple myeloma accounts 14 %, lymphoid leukemia 11 %, and Hodgkin's lymphoma accounts for 5 % of PTLD [12, 114].

As with other malignancies, immunosuppression is an important risk factor for PTLD. Solid organ transplants that require a greater level of immunosuppression, such as heart, lung, and intestine, have a higher incidence of PTLD (20–25 %). However, specific agents targeting T cells, such as ATG, OKT3, CNI, and recently belatacept, have been found to disproportionately increase risk [115, 116]. Belatacept is especially interesting as rejection episodes are more frequent in belatacept-treated patients, suggesting that PTLD in these patients is not always an effect of net immunosuppression [117, 118]. Besides immunosuppression, EBV infection is another major factor in the development of PTLD. Nearly 50–70 % of all cases of PTLD are associated with EBV infection. This is especially true when the transplant recipient is EBV seronegative. In situations where an EBV seronegative patient receives an organ from an EBV positive donor, the risk of PTLD is increased up to six times [119, 120]. EBV seronegative status is especially problematic when using belatacept. Due to the higher risk of PTLD, especially central nervous system (CNS) PTLD, the use of belatacept is contraindicated in EBV seronegative recipients.

PTLD has been found more likely to occur in patients < 10 years of age and those > 60 years. The older population is at higher risk of malignancy overall, and younger

patients may be more likely to be EBV seronegative. There is also emerging data revealing genetic risk factors for developing PTLD. Numerous human leukocyte antigen (HLA) types have been suggested to either predispose to or protect from PTLD. Cytokine gene polymorphisms involving TGF-β, INF-γ, TNF-α, are also reported to have a role in pathogenesis. Caucasian race, pretransplant malignancy, and viral infections such as cytomegalovirus (CMV) and HHV-8 have been proposed as additional risk factors [114, 116, 121, 122].

After EBV infection, a group of latent B cells with downregulated antigen expression arise which escape immune surveillance. These cells, in the presence of waning immunity, can proliferate and lead to lymphoproliferative disease. EBV encoded proteins, such as LMP-1 and LMP-2A, transmit signals that can mediate B cell activation. LMP-1 engages the signaling proteins from the tumor-necrosis-factor receptor-associated factors (traFs) that lead to cell growth and transformation. Proteins like EBNA-2 and EBNA-LP, which are both nuclear proteins, upregulate pro-growth factors such as c-Myc. Together they can transform B cells into immortal lymphoblastoid B cells [123].

As previously mentioned, cytokines such as IL-10, IL-6 also have a central role in the pathogenesis of PTLD. PTLD can be donor or host derived. Donor-derived variant is more likely to involve the allograft.

PTLD is usually of B cell origin, with only 5 % of all tumors being of the T cell and T cell/NK cell origin. The majority of B cell PTLDs are EBV positive (60–70 %), while 90 % of the T cell PTLDs are EBV negative. EBV negative PTLD usually is of late onset, and believed to be less responsive to therapy [114, 124].

The WHO classification identifies four types of PTLD:

1. *Plasmacytic hyperplasia and infectious mononucleosis-like PTLD*
2. *Polymorphic PTLD*
3. *Monomorphic PTLD*
4. *Classic Hodgkin's lymphoma*

While earlier reports suggested that PTLD occurred early posttransplant (< 1 year), more recent data depict a later onset with a median time of 32–76 months posttransplantation [125, 126]. This change is believed to be due to the increased recognition of EBV negative PTLD [12]. Common symptoms of PTLD include fever, lymphadenopathy, weight loss, anorexia, fatigue, and organ dysfunction. Extranodal involvement is relatively common, and includes sites such as lung, skin, bone marrow (BM), and CNS with the gastrointestinal tract being the most common extra nodal site. PTLD can also involve the allograft itself, and can masquerade as a rejection or enlarged allograft [114, 124].

Laboratory abnormalities include anemia, thrombocytopenia, elevated LDH, hyperuricemia, monoclonal protein in the serum and urine, and signs of graft dysfunction. Diagnosis usually requires an excision biopsy of the lymph node, rather than a fine needle aspirate. Biopsy specimens should be evaluated for EBV infection. Imaging techniques such as CT scans of the chest, abdomen, and pelvis or positron emission tomography (PET) scans are used for staging similar to traditional lymphoma staging [114, 124]. EBV viral load monitoring may have a role in the

diagnosis of PTLD. The American society of transplantation recommends checking monthly EBV viral loads for EBV negative recipients up to 1 year posttransplantation [127]. While EBV PCR can be predictive of developing PTLD, it should be noted that PTLD can also develop in the absence of detectable EBV viral load [128, 129]. Monitoring of viral load has inherent disadvantages, such as a lack of consistency between testing methods, lack of universal reference standard, and differing peripheral blood specimens used [130].

Case #6 Follow-Up and Discussion
The correct answer is choice c. For B cell PTLD reduction in immunosuppression and early rituximab is the mainstay of therapy. A detailed discussion follows below.

The goal of treatment, as with almost any tumor posttransplant, is to achieve cure while preserving allograft function. There are various therapeutic strategies which are used, including reduction in immunosuppression, antiviral therapy, rituximab, and chemotherapy. The choice of therapy should consider the aggressiveness of the disease. Various therapies are discussed below.

1. Reduction in immunosuppression.

Reduction in immunosuppression is the mainstay of PTLD therapy. This may be sufficient to treat early disease such as type 1 and 2 PTLD. CNI have been incriminated in the pathogenesis of PTLD, and their target levels should be reduced. Interestingly, the use of mycophenolate mofetil has not been shown to increase the risk of developing PTLD, however, it is usually stopped after diagnosis. The response to therapy usually takes several weeks, and has an inherent risk of precipitating allograft rejection. Response rates are variable, with around 31–37 % achieving complete remission. Rejection rates approximating 39 % have been described. Factors that portend nonresponse to reduction in immunosuppression alone include elevated LDH, older age, B symptoms, multiorgan involvement and/or organ dysfunction [131, 132].

2. Antiviral therapy

In some studies, antiviral therapy with ganciclovir and acyclovir has been shown to reduce the incidence of PTLD. However, the use of antiviral agents as a treatment strategy for PTLD is not convincing [133]. These nucleoside analogs require the viral kinases to be in the active cytotoxic forms which are expressed in the lytic phase rather than the latent phase. To induce the viral lytic phase, agents such as arginine butyrate have been tested, but more data is needed before such a strategy can be recommended [123, 134].

3. Rituximab

Rituximab is a chimeric monoclonal anti-CD20 antibody. It is very useful in CD20 positive PTLD. It may be used for both polymorphic and monomorphic lesions.

Rituximab used as a single agent has been shown to result in a complete remission in 20–40 % of patients [114, 135, 136]. More recent studies seem to advocate the early use of rituximab concomitant with reduction in immunosuppression [136, 137]. Rituximab has also been used as a preventive strategy upon detection of EBV genome copies in the serum [138]. The most commonly used dosing regimen for rituximab is 375 mg/m^2 per week for 4 weeks [137].

4. Chemotherapy

Chemotherapeutic options include cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and dose-adjusted doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP). The response rate to chemotherapy is highly variable, with rates of complete remission ranging from 30–50 %; however, treatment related complications are also up to 50 % in some studies [139–142]. Chemotherapy can be administered by itself or in conjunction with rituximab to patients with CD20+ PTLD. In one such study, combination of rituximab and CHOP resulted in an overall response rate of 90 %, with a complete response rate of 68 % [143].

5. Radiation therapy

Radiation therapy may be used for localized disease or CNS involvement. It is usually used in conjunction with reduction in immunosuppression [144, 145].

6. CNS lymphoma

For isolated CNS lymphomas, the different treatment options include radiation therapy, chemotherapy with or without rituximab, and particularly high dose methotrexate. Again, treatment is accompanied by a reduction in immunosuppression [146–148].

7. Adoptive immunotherapy

Infusions of donor-derived EBV-specific cytotoxic T cells, autologous EBV-specific T cells, and partially matched unrelated allogeneic EBV-specific T cells have also been suggested as treatment strategies [149, 150].

The role of re-transplantation after a diagnosis of PTLD is controversial, as reintroducing high levels of immunosuppression may result in recurrent disease. However, patients with a history of PTLD have been successfully re-transplanted with favorable outcome. The best evidence of this practice comes from an OPTN/UNOS database analysis by Johnson [151]. From 1987 to 2004, 69 solid organ recipients, of which 27 had a kidney transplant, underwent re-transplantation after a diagnosis of PTLD. At a median follow up of 742 days, all kidney transplant recipients were alive and graft survival was 88.9 %. Importantly, the median time to re-transplantation from diagnosis of PTLD was 1337 days, suggesting that timing of re-transplantation may be important to optimize outcome.

Case #7
You are consulted by a colleague at another transplant center for advice regarding an organ offer. He has received two organ offers for a highly sensitized patient. Donor 1 had a history of lung cancer 4 years ago, and donor 2 had a history of prostate cancer treated 3 years ago. Donor 1 had a normal chest X-ray during the hospitalization, and donor 2 had a recently normal prostate specific antigen. Besides the history of malignancy, both donors are otherwise healthy and equally matched to the recipient. The potential recipient is well informed and aware of the risks of donor-origin malignancy. Which of the following statements would you suggest?

a. Mortality from donor-derived cancer is very low and both donors are acceptable.
b. Donor 1 is a better offer because a longer time period has passed since cancer treatment.
c. Donor 2 is a better offer because prostate cancer is an unusual donor-derived cancer.
d. Both donors are at a high risk for transmitting cancer.

Donor-Derived Malignancies

The risk of cancer transmitted from a donor is rare, but real. In a recent paper from the UK among more than 30,000 transplants, there were 18 recipients who developed cancer of donor origin from 16 donors (0.06 %). In none of the donors was the diagnosis of cancer apparent at the time of donation. These cancers were either donor transmitted (transmitted with the graft) or donor derived (develop subsequently from the graft). In this study, there were 15 donor transmitted cancers with 6 cases of RCC, 5 cases of lung cancer, 2 cases of lymphoma, 1 case of neuroendocrine cancer, and one case of colon cancer. There was a 20 % mortality rate in these recipients as a direct consequence of the donor-derived cancer. Outcome was better if the cancer was identified early (< 6 weeks) [152]. An earlier report from UNOS revealed a 45 % transmission rate from donors who were subsequently identified as having a cancer. Cancers transmitted include melanoma, lung, breast, colon, kidney, KS, and glioblastoma multiforme, while transmission of nonmelanoma skin cancers and primary CNS tumors is very rare [153]. Most recently, a systematic review was conducted, looking at all of the published evidence regarding donor-cancer transmission in kidney transplant recipients. The authors found that the most common transmitted cancer types were RCC, followed by melanoma, lymphoma, and then lung cancer. Recipients of donors with melanoma and lung cancers had greater than 50 % mortality at 24 months posttransplant, while recipients with transmitted renal cell cancers had the best survival, with a mortality rate of under 30 % at 24 months

posttransplantation. In this analysis there were no reported cases of donor-derived prostate cancer [154].

Management of donor-derived cancer includes reduction in immunosuppression, excision of the tumor, transplant nephrectomy, chemotherapy, and radiation [102, 152, 155]. When discovered before spread, patients should be strongly advised to have the graft explanted.

Case #7 Follow-Up and Discussion
The correct answer is choice c. Donor transmission of prostate cancer is very unusual while lung cancer is one of the most common types of donor-transmitted cancer.

Transplantation in Patients with Preexisting Malignancy

The final aspect of this chapter focuses on transplantation in patients with preexisting malignancy. In an early study from the University of Cincinnati, patients who had cancer before transplantation were found to have a cancer recurrence of 22 %. The rate of recurrence varied, based on the time period they were treated before transplantation, with those treated within 24 months prior to transplantation having the highest recurrence rate [156]. Similar findings have been seen in a more recent study, with lower recurrence rates among those who have had a longer disease free period before transplantation [157]. Recurrence rate also depends on the type of tumor. Among those cancers treated pretransplantation, the highest rate of recurrence is with breast carcinomas (23 %), symptomatic renal carcinomas (27 %), sarcomas (29 %), bladder carcinomas (29 %), nonmelanoma skin cancers (53 %), and multiple myeloma (67 %) [158]. Lymphomas, on the other hand, have a recurrence rate of around 10 % [126]. Recurrence of malignant melanoma varies by stage. For patients with prior stage II or III melanoma, most experts recommend a disease free interval of 5–10 years [156, 159].

The history of cancer prior to transplantation is also a predictor of increased mortality after transplantation. One study revealed a 30 % increase in mortality in patients with pretransplant cancer. The increase in mortality is particularly seen in non-kidney solid organ transplants [160]. Due to the variability in recurrence recommendations for placement on transplant waiting lists differ by the type of cancer. For low grade cancers such as basal cell carcinoma (BCC), low grade bladder, in situ carcinomas, focal neoplasms, and incidentally discovered RCC, no waiting period is required. However, for tumors such as breast or colorectal carcinoma, a disease free period of 5 years is recommended before transplantation. Symptomatic large RCC (> 5 cm), or those with invasion may require a 5 year waiting period [161].

For most other tumors, a cancer free period of approximately 2 years is recommended [156, 159].

Multiple myloma, monoclonal gammopathy of undetermined significance (MGUS) and associated plasma cell dyscrasias require further discussion as these disorders often lead to ESKD themselves. In patients with pretransplant MGUS one study with a median follow-up of 8.5 years found that 8.7 % progressed to smoldering myeloma while no patient progressed to malignant myeloma. The authors of the same study found that out of 19 patients who developed MGUS after transplant, none progressed to myeloma. There were however, two cases of lymphoma in each group [162]. This data suggests that it is reasonable to transplant patients with MGUS with close hematology follow-up. Patients with light chain deposition disease (LCDD) may be an exception to this strategy. One study found that five out of seven patients with LCDD had recurrence of renal disease between 2 and 45 months posttransplant [163]). Such patients should not be transplanted unless they have documented resolution of abnormal light chain production. Finally, limited data exists on the optimal timing of transplantation after remission of multiple myeloma. As mentioned previously, one report suggests a recurrence rate of 67 % after transplantation, although treatment strategies for myeloma have greatly changed from the time of study publication [155]. Current data suggest better long-term mortality after multiple myeloma, especially in patients under the age of 60, and better genetic markers to risk stratify myeloma [164]. Based on these findings, we suggest kidney transplantation in young patients with minimal comorbidities after careful consultation with a hematologist to understand the individual mortality and recurrence rate. Waiting 2 years after remission appears reasonable in most cases. Finally, a particularly attractive option is performing a combined bone marrow and kidney transplant from the same donor. This has been accomplished with reasonable outcomes in a small number of patients [165]. Currently this strategy should not be pursued except within a clinical trial (clinicaltrials.gov).

In summary, regardless of the type of malignancy, close discussion with an oncologist is recommended prior to transplanting patients with a history of cancer. For tumor-specific questions the Israel Penn registry is a valuable consultation tool (http://ipittr.uc.edu/).

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Chapter 17
Cancer, Palliative Care and Acute Kidney Injury: The Hard Decisions of Offering or Not Offering Dialysis

Ritu K. Soni and Jane O. Schell

List of Abbreviations

ACP	Advance care planning
AKI	Acute kidney injury
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
ESKD	End-stage kidney disease
RRT	Renal replacement therapy

Case #1
MJ is a 78-year-old Caucasian female with a known history of hypertension and chronic obstructive pulmonary disease (COPD), and a recent diagnosis of anal squamous cell cancer with vaginal and bladder metastases, who is admitted to the gynecology service for scheduled surgery. She undergoes total pelvic exenteration with end colostomy and creation of an ileal conduit urinary diversion. On the third postoperative day, she develops oliguric acute kidney injury, which is attributed to acute tubular necrosis due to intraoperative hypotension.

How might this patient do if renal replacement therapy is initiated?

Dialysis decision-making in patients with cancer and acute kidney injury (AKI) poses a challenge to nephrologists, as these patients are older with multiple

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comorbidities. For those patients with advanced cancer, the burdens of dialysis may outweigh hoped-for benefits. These considerations are especially germane as the median age of patients with a cancer diagnosis is 66 years [1]. A majority of these patients are already at risk for kidney disease by virtue of their age and underlying comorbidities, and have additional risk from the burden of cancer and its treatment. There is a growing recognition of the added risk of AKI in patients with cancer in comparison with those without cancer [2–7]. Furthermore, as cutting-edge cancer therapies continue to improve cancer-free survival, resulting in increasing numbers of cancer survivors, the incidence of kidney diseases is only expected to rise in this subpopulation.

Cancer patients with kidney disease represent a complex population with unique care needs. Treatment decisions require consideration of drug choice, potential dose adjustments, and minimization of side effects and toxicities [8]. In addition, these patients are at risk for burdensome symptoms, both physical and psychological, that may impact quality of life and overall morbidity. For patients whose survival may be limited by their cancer diagnosis, decisions regarding dialysis initiation require consideration of the overall clinical trajectory. By addressing these needs, cancer patients with kidney disease can benefit from an interdisciplinary care approach.

In this review, we focus on the management approach for cancer patients with kidney disease who may do poorly, especially with dialysis. We present the latest data in outcomes of AKI and dialysis in hospitalized patients, focusing on cancer patients when the data exist. We provide a framework for treatment-related decision-making with patients and family when uncertainty exists with an emphasis on early introduction of palliative care services. Finally, we further discuss the transition to more active management of symptoms and support at the end of life with hospice services.

Outcomes of AKI in Patients with Cancer

Incidence of AKI and CKD in Cancer

The exact epidemiology of both acute and chronic kidney diseases (CKD) in patients with cancer is not clearly known. Most studies examining kidney disease in patients with cancer have been either conducted in the setting of critical illness [9–12] or restricted to certain types of cancers [7, 11, 13–15]. However, longitudinal data of AKI risk exist in patients with cancer. In a population-based cohort study in Denmark, 37,267 incident cancer patients were followed up for 5 years to determine the incidence of AKI in patients with cancer [2]. The 1-year and 5-year risks of developing AKI (defined as more than 50 % increase in serum creatinine) were 17.5 and 27 %, respectively, with the risk being the highest among those with renal cancer, liver cancer, and multiple myeloma (44, 33, and 31.8 %, respectively). In a recent analysis of data collected of 3558 patients admitted to the University of Texas MD Anderson Cancer Center over 3 months in 2006 by Salahudeen et al., 12 % had AKI by

RIFLE (risk, injury, failure, loss, and end-stage renal disease) criteria, with severity in the risk, injury, and failure categories of 68, 21, and 11 %, respectively. Nephrology consultation was obtained in 10 % of patients and dialysis was required in 4 % [3]. In a study by Lahoti et al. in patients with cancer from the same institution, 36 % of patients undergoing induction chemotherapy developed AKI [16]. The prevalence of CKD in patients with cancer is variable in different studies, ranging from 16.6 to 64 % [17–20]. These epidemiological data, although limited, underscore the high risk of renal dysfunction in patients with cancer.

While the exact incidence of AKI in cancer patients is not known, clinical experience and limited existing data suggest that the rate of AKI incidence might be higher in cancer patients than noncancer medical patients. The impact of AKI in cancer patients on health-care utilization is also less clear. Cost analyses of AKI in patients with or without cancer demonstrate correlation of AKI with longer hospitalization and higher hospital costs [3, 13, 21, 22]. One analysis from the Nationwide Inpatient Sample reported an incremental increase in average costs and duration of hospitalization in cancer patients without AKI, AKI without renal replacement therapy (RRT), and dialysis-requiring AKI to be $ 13,947, $ 25,638, and $ 44,619; and 7.4, 12.2, and 17.6 days, respectively [22]. In another study conducted in a comprehensive cancer center, patients with AKI had a 100 % increase in the length of hospital stay and a 106 % increase in the hospital costs [3]. Lahoti et al. reported a 21 % increase in hospital costs for patients who received dialysis [13]. These findings highlight the health-care burdens associated with AKI in hospitalized patients with AKI.

Outcomes of AKI in Cancer

It is widely accepted that AKI is associated with poor outcomes in critically ill patients and is associated with significant morbidity and mortality [23]. However, limited data exist examining the long-term outcomes of AKI with or without RRT in patients with cancer. While historical studies demonstrate poor survival outcomes with RRT in patients with malignancy and AKI [24–27], more recent trials suggest that mortality risk in these patients is independent of underlying malignancy and is more associated with overall health status and coexisting comorbidities [6, 28].

A large prospective cohort study by Soares et al. indicated that the 6-month survival rate in cancer patients who require dialysis for AKI is comparable to those without cancer [6]. Of the 309 patients who developed renal dysfunction, 32 % initiated dialysis and ultimately 82 % of those who experienced AKI recovered. Long-term outcomes however were less promising as 6-month survival among those with renal dysfunction was only 27 %. Only 6 % of these survivors required long-term chronic maintenance RRT. The researchers also observed that the timing of dialysis initiation was associated with mortality. Among the patients who underwent dialysis, survival rates were high in those who received RRT on the first day of admission to the intensive care unit (ICU) compared with those who received dialysis thereafter (36 % vs. 14 %, respectively; $P = 0.03$), with a 100 % mortality rate in those who were initiated on RRT after the fourth day of ICU admission [6]. These

results argue that the presence of underlying cancer should not preclude the option of RRT in this subpopulation. In addition, a majority of patients with AKI requiring dialysis may actually recover kidney function.

A single-center, retrospective study performed in Belgium further confirms the findings of Soares and group [28]. Thirty-two cancer patients with AKI requiring RRT were treated with continuous dialysis, of which 65.6 % regained renal function either completely or partially. Based on these findings, the authors concluded that acute renal failure could be successfully treated with RRT in patients with cancer. Furthermore, they demonstrated that continuous venovenous hemodiafiltration (CVVHDF) is an effective modality for treating these patients [28]. Although patients with hematological cancers have a high incidence of AKI compared with those without cancer [5], the adjusted 6-month mortality in critically ill patients requiring RRT is independent of the presence of underlying malignancy [5, 9, 10]. In another study, data of 199 consecutive cancer patients, most in septic shock treated with continuous dialysis at University of Texas MD Anderson Cancer Center, were analyzed [29]. Despite excellent dialysis, the sequential organ failure assessment (SOFA) score remained predictive of mortality. By day 30 of continuous dialysis, 130 of the 199 patients died, yielding a 30-day mortality rate of 65 %. Twenty-two patients (11 %) had died within 24 h of starting the sustained low-efficiency dialysis in the continuous mode (C-SLED). Of the patients who died within 30 days of starting the dialysis, 76 had been withdrawn from life support because of the irreversible nature of their illnesses. The median survival time of all patients was 15 days (95 % confidence interval, 11–21 days) from the start of dialysis. Among patients who survived 30 days, 65 % had experienced renal recovery from AKI, defined as not requiring further dialysis support. Clearly, without promptly instituting dialysis, few patients would have survived. The data suggest that in critically ill cancer patients with AKI, short-term survival is possible with dialysis at a rate comparable to critically ill noncancer ICU patients. The data also suggest that for patients deemed irreversibly ill in spite of a short trial of dialysis, the decision to withdraw dialysis is justified.

Prognostic Factors of AKI in Hospitalized Patients

An expanding body of literature has identified numerous inherent and acquired factors associated with poor clinical outcomes in these patients. For those patients with AKI not requiring dialysis, the greater severity of renal dysfunction was associated with higher mortality [4, 6, 9, 12, 16, 24–27, 30], although a few more recent trials have refuted this association [11, 28]. Other predictors of mortality include many factors independent of underlying cancer, including etiology of AKI [11], ICU days until initiation of dialysis [9], sepsis [4, 31], use of vasopressors [4], acute respiratory failure [4, 30–32], liver failure [30], number of accompanying organ dysfunctions [6, 9–11, 28, 30, 32, 33], older age [6, 9], comorbidities [9], and functional capacity [6, 32], to list a few. However, the active cancer status has also been associated with mortality [6, 32].

For cancer patients with AKI, dialysis decision-making should largely be considered independent of cancer diagnosis. There are however limitations and discrepancies in the aforementioned studies in relation to the outcomes of RRT in cancer patients, which may be explained on the basis of heterogeneity in study populations, differences in dialysis modality, types of cancers, status of underlying cancers, comorbidities, and low statistical power in some trials. It is also noteworthy that most of these data are synthesized from critically ill patients with hematological cancers [5, 10, 24–27, 31], and whether these results can be extrapolated to all cancer patients needs to be further investigated. Collectively, these data suggest that if timely instituted, dialysis can benefit selected patients with cancer and AKI, substantiating early nephrology involvement in their care. The decision to initiate dialysis in these hospitalized patients must include consideration for the entire clinical picture as well as the etiology for the kidney injury.

Long-Term Outcomes with and Without Dialysis

Dialysis is considered as a lifesaving therapeutic modality with the potential to prolong survival. For patients with high comorbidities and advanced age, dialysis may confer more risk than hoped-for benefit. In fact, a growing body of literature suggests that a conservative (non-dialytic) management should be considered as treatment options for such patients. For example, in elderly patients with advanced cardiovascular disease, survival was not statistically different between those on dialysis and those treated conservatively [34–38]. In addition, other studies have examined how patients who either started dialysis or were managed conservatively spent their time. In an observational study of patients treated with RRT or conservative management, survival was more in the RRT group (37.8 months vs. 13.9 months, $P < 0.01$), however patients conservatively treated experienced more hospital-free days than those on RRT (0.069 vs. 0.043 hospital days/patient days survived) [39].

In addition to survival, the benefits of RRT must also include aspects of quality of life. The impact of RRT on self-reported quality of life, symptom burden, and functional status has not been well studied in patients with cancer on dialysis. Data from the general population however indicate a detrimental effect of dialysis initiation on the functional status of older adults, independent of age, gender, ethnicity and pre-dialysis performance status [40]. A UK-based study prospectively measured health-related quality of life and life satisfaction in patients with CKD who opted for RRT compared with those managed conservatively without dialysis [41]. While survival was better in the RRT group, quality of life was maintained in those managed conservatively, and life satisfaction declined significantly after commencement of RRT [41]. Patients who elect conservative management typically prefer treatment focused on quality of life rather than quantity. These patients are older (median age 80 years) with multiple comorbidities and personal preferences focused more on conservative treatments [42].

Prognostication for long-term dialysis, similar to dialysis in the setting of AKI, involves consideration of underlying comorbidities and overall health status. Cohen and colleagues developed and validated a clinical prediction tool for estimation of 6-month prognosis of patients undergoing hemodialysis. This tool incorporates the subjective variable, the surprise question ("Would I be surprised if this patient died in six months?") with established four independent predictors of early mortality (low albumin level, older age, peripheral vascular disease, and dementia) [43]. These tools are estimations of survival and should be interpreted within the clinical context of an individual patient. Such tools can be instrumental in identification of those with poor prognosis, and who may benefit from early introduction of palliative care.

When assessing the benefits of long-term RRT in patients with cancer, it is imperative to take into consideration the factors such as age, performance status, severity of concomitant organ failures, and status of the underlying cancer. In this respect, consideration for long-term decision-making of RRT in these patients is similar to other patients with advanced comorbidities without cancer. In the elderly population, comorbidity index should be one of the major considerations in the decision-making for RRT versus conservative management, with particular concern for ischemic heart disease. In addition, consideration for not only potential survival benefit of dialysis but also the patients' underlying goals in terms of quality of life should be made.

Case Continued

MJ's medical course over the next week is further complicated by ventilator-associated pneumonia and presumed sepsis. She is mechanically ventilated and maintained on vasopressors. She develops anuric AKI with refractory metabolic acidosis. Her son is her medical decision-maker. Prior to this hospitalization, patient had been living independently and enjoyed quality time with her family and friends. He believes his mother would want to undergo treatments such as dialysis in hopes of resuming her prior quality of life.

How to approach discussions of dialysis decision-making in a patient who may do poorly on dialysis?

Communication and Dialysis Decision-Making

In high-risk populations such as cancer patients, dialysis decision-making involves weighing both the risks and benefits and their potential impact on survival and quality of life. Once there is a sense of how the patient is likely to do on dialysis, the challenge becomes how to elicit the patient's goals and values. Through eliciting these goals and values, the clinician can better know whether dialysis is likely to achieve these goals and whether it is consistent with patient's goals.

Table 17.1 Gaining an understanding of the patient's goals and values

Invitation to assess readiness to have conversation: "Can we talk about how things have been going with your kidney disease?"
Using open-ended "big-picture" questions to assess care goals and preferences: "What is life like outside the hospital?" "What is most important to you now?" "What are you hoping for?" Outline barriers to decision-making: "As you think about the future what worries you most?"
Propose a plan that meets the patient's goals: "Now that I understand what's important to you, can I make a recommendation?"

Gaining an Understanding of the Patient's Goals and Values

Understanding the patient's goals and values allows the clinician to learn how a patient perceives and views their illness and health condition. These *big-picture* goals and values are best elicited through using open-ended questions exploring the patient's understanding of disease, hopes for the future and concerns that may influence decision-making (Table 17.1). By framing dialysis in terms of achieving specific goals, there are defined milestones for which future discussions regarding the benefits of dialysis can be revisited. Finally, exploring patient's concerns in the context of dialysis decision-making can expose potential barriers to decision-making. These concerns include physical suffering, spiritual crises, or worries about leaving loved ones.

These conversations often arouse feelings of uncertainty and strong emotions. Just as important as providing necessary medical information, the clinician must also recognize and respond to patients' emotional concerns. Unattended emotion is associated with distress and may impact a patient's ability to process information and meaningfully participate in discussions of decision-making [44]. Table 17.2 includes examples of patients' responses to affective concerns and dealing with uncertainty [45, 46]. Acknowledging emotion allows providers to move forward with discussions in a way that patients can process the information and fully participate in decision-making [47].

Giving a Recommendation

After consideration of the medical facts and the patient's *big-picture* goals, the provider can offer a recommendation regarding dialysis. This recommendation must consider the balance of potential benefits and burdens of dialysis, from the patient's point of view. For patients who are critically ill, the decision may be to focus on comfort and not initiate dialysis. In the case of clinical uncertainty, the decision

Table 17.2 Empathic responses to affective concerns

Responding to emotional concerns (verbal empathy): N-U-R-S-E
*N*ame the emotion: "You seem worried"
*U*nderstand: "I can understand this is disappointing"
*R*espect: "You have shown a lot of strength"
*S*upport: "We will get through this together"
*E*xplore: "Tell me more"
Responding to uncertainty:
Name the uncertainty
Respond to emotional response
Offer support, "What can we do for you given we don't know for sure how things will go?"
Reassure your commitment, "I'll stick with you throughout this"

may involve proposing a trial of dialysis for a period of time in hopes of achieving proposed clinical and quality of life milestones.

Time-limited trials are beneficial when there is a medical uncertainty. Through defining a trial of treatment, the provider can outline a plan which names the goals of the patient and a meeting time to assess whether these goals are being achieved with the current plan. Just as important as outlining the success with dialysis, providers should also outline what may happen if things do not go as desired. This sets up the opportunity to initiate advance care planning (ACP) and elicit end of life preferences.

Case Continued

MJ is started on continuous renal replacement. She clinically improves and is transitioned to intermittent hemodialysis three times a week through a tunneled dialysis catheter. She is transferred to a skilled nursing facility for continued physical therapy and rehabilitation. She complains of persistent fatigue, which is worse after dialysis sessions. She has significant pain in her lower extremities concerning for neuropathy related to prior chemotherapy, further limiting her functional capacity. After two hospitalizations for infections related to her dialysis catheter, she becomes bedbound and requires assistance in all her activities of daily living.

How to manage a dialysis patient who is clinically declining?

Role of Palliative Care in Cancer Patients with AKI

Care of the cancer patient with kidney disease may be optimized through involvement of palliative care services and ongoing communication between oncology and nephrology care team. Palliative care is an interdisciplinary team composed of physicians, nursing services, social workers and chaplains that can provide symptom management and ACP with timely transition to hospice services when appropriate.

In patients with advanced non-small cell lung cancer, early palliative care in addition to standard oncologic care resulted in improved quality of life and decreased incidence of depression [48]. Patients with kidney disease, independent of cancer, suffer from comparable burdens and mortality risk, as do patients with cancer. Therefore, early attention to palliative care domains, such as symptom management and ACP, is warranted.

Symptom Management

Symptoms in CKD, with or without dialysis, are common and independent of cancer diagnosis. These patients suffer from a substantial burden of debilitating physical and psychological symptoms resulting in significant impairment in their quality of life [49–52]. Yet, over 50 % of these symptoms are undertreated [53]. Fatigue and pain are the most commonly encountered symptoms, others being pruritus, depression, nausea and vomiting, sleep disturbances, muscle cramps, anorexia and sexual dysfunction [54–56]. Data suggest primary care providers may prescribe pharmacologic therapy, particularly for emotional symptoms, rather than nephrologists [53]. Considering the increasing prevalence of end-stage kidney disease (ESKD), the momentous burden of distressing symptoms in these patients and their impact on overall quality of life, it is crucial for both nephrologists and primary care providers to have a better understanding of symptom management in order to provide patient-centered care. Tables 17.3 and 17.4 briefly outline the guidelines for symptom management in advanced CKD [55–58]. Additional attention must be paid to medication dosing with appropriate adjustments for the degree of renal impairment.

Advance Care Planning and Hospice Services

One of the important components of the comprehensive treatment plan for patients with kidney disease, particularly those with cancer, is ACP. ACP encompasses dynamic, ongoing communication among physicians, patients, and their families addressing the patient's goals for care, including preferences for end of life care [59]. The limited life expectancy in patients with ESKD, either with or without dialysis, warrants early initiation of ACP [60]. Timely instituted discussions regarding goals of care allow patients to better understand their illness and develop a realistic perspective about the role of intensive medical interventions. Patients who engage in these discussions tend to undergo less intensive care and fewer life-prolonging therapies and are more likely to enroll in hospice care in their final week of life. Furthermore, longer hospice stays (> 1 week) are associated with better quality of life in patients, which in turn is associated with an improvement in self-reported quality of life and lower incidence of depression among surviving caregivers during the bereavement phase [61].

Table 17.3 Analgesia in end-stage renal disease

Drug	Rationale for recommendation/metabolic considerations	Dose adjustment for ESKD	Additional comments
Safe			
Acetaminophen	Safe alternative to NSAIDs	No	For mild-to-moderate pain, exhibit caution if coexistent liver disease
Fentanyl	Hepatic metabolism, no active metabolites	Yes	Opioid of choice
Methadone	Excreted in feces, no active metabolites	Yes	Opioid of choice
Use with caution			
Tramadol	Ninety percent metabolites excreted by kidneys	Yes	Risk of serotonin syndrome with selective serotonin reuptake inhibitors
Oxycodone	Hepatic metabolism. Less than 10 % renally excreted, limited data on safety in CKD	Yes	For moderate-to-severe pain
Hydromorphone	Active metabolite is renally excreted. Monitor for neurotoxicity, myoclonus	Yes	For severe pain
Gabapentin	Excreted unchanged in urine. Accumulation in CKD can cause somnolence, dizziness, and gait disturbances	Yes	For neuropathic pain
Not recommended			
Nonsteroidal anti-inflammatory agents (NSAIDs)	Risk of gastrointestinal bleeding, hypertension, fluid retention. Decline in residual renal function in peritoneal dialysis	Avoid use	–
Morphine	Active metabolites are renally excreted; accumulation in CKD can cause neurotoxicity, seizures, and central nervous system and respiratory depression	Avoid use	Can be used with caution in terminal patients
Meperedine	Active metabolite is renally excreted, accumulation in CKD can cause neurotoxicity, seizures	Avoid use	–

Table 17.4 Non-pain symptom management in end-stage renal disease

Symptom	Management
Fatigue	Optimize dialysis dose to ensure adequate clearance
	Treat anemia with intravenous iron and/or erythropoietin
	Encourage regular exercise and physical therapy
	Evaluate for and treat depression
	Evaluate for and treat sleep disturbances
Pruritus	Optimize dialysis dose to ensure adequate clearance
	Treat secondary hyperparathyroidism
	Reinforce adherence to phosphate binders and low-phosphorus diet
	Use emollients, oral antihistamines
	Other treatment options include neurontin, capsaicin cream, and phototherapy with UVB light
Sleep disturbances	Encourage sleep hygiene
	Avoid caffeinated beverages, tobacco, or alcohol in the evening
	Evaluate for and treat sleep apnea
	Treat with benzodiazepines once sleep apnea is ruled out
Anorexia	Optimize dialysis dose to ensure adequate clearance
	Evaluate for and treat depression
	Treat nausea with antiemetics
	Minimize anticholinergic agents to prevent dry mouth
	Trial of zinc supplementation to treat taste disorders
	Trial of appetite stimulants (e.g., megestrol, low-dose mirtazapine)
	Overall assessment of clinical status
Nausea and vomiting	Optimize dialysis dose to ensure adequate clearance
	Treat with antiemetics (ondansetron and metoclopramide)
	Trial of haloperidol for refractory nausea
Sexual dysfunction	Evaluate for and treat hormonal dysregulation (low testosterone levels, hyperprolactinemia)
	Evaluate for and treat depression
	Trial of phosphodiesterase inhibitors if not contraindicated

Despite the increasing recognition of the need for ACP in the dialysis population, only a minority of them have written advance directives [62, 63]. The end-of-life experience for dialysis patients is likely a reflection of inadequate ACP. Wong et al. [64] examined treatment intensity and outcomes in dialysis patients during the last month of life. Dialysis patients were more likely to undergo intensive therapies, including admission to ICU, and less likely to receive appropriate hospice services compared to those with cancer and heart failure.

Timely transition to hospice services is a mechanism for optimal palliative care to deliver quality symptom control, psychological support to patient and family, and comfort at end of life. Improving hospice delivery to patients with ESKD is a worthy mission as these services are heavily underutilized by ESKD patients [65]. Chronic dialysis-dependent patients who withdraw from dialysis, dialysis patients with a nonrenal terminal illness, and patients with ESKD who opt to not initiate dialysis and have an estimated life expectancy of less than 6 months are eligible for hospice services and should be timely referred by nephrologists or primary care providers. Palliative care services however should be an option for any patient with kidney disease who has needs.

Case Conclusion
MJ's mental status limited her cognitive ability and capacity to communicate. Her son worried about whether his mother had potential for any recovery and whether or not she was suffering. After a frank discussion with the patient's nephrologist about MJ's prognosis and overall values, her son elected to withdraw dialysis and initiate hospice services. His wishes were respected, and the patient passed peacefully 7 days later receiving low doses of hydromorphone for pain and shortness of breath.

Conclusion

Decision-making regarding initiation and withdrawal of RRT in critically ill patients is very challenging. Despite increasing awareness of the high risk of AKI in patients with cancer, data on long-term outcomes in these patients are limited. Dialysis decision-making in these patients should take into account the patient's overall clinical condition and comorbidities, rather than an underlying diagnosis of cancer. MJ's case illustrates the opportunity to initiate earlier palliative care for symptom management and early initiation of ACP to guide end-of-life decision-making. Although, in this case, hospice services were initiated in the last days of life, nephrologists have a responsibility to identify and respond to patient needs along the disease trajectory in a timely manner. For cancer patients with kidney disease, early initiation of palliative care, communication regarding ACP, and timely referral to hospice care, when appropriate, are key to patient-centered management.

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Appendix

Appendix: Concept Maps

The following five concept maps are descriptive diagrams drawn by Kenar Jhaveri, editor of the book, to help simplify the complex topics covered in the book. All of the five concept maps have appeared on the editor's blog www.nephronpower.com and are reproduced here for this book with permission (Figs. 1, 2, 3, 4, and 5).

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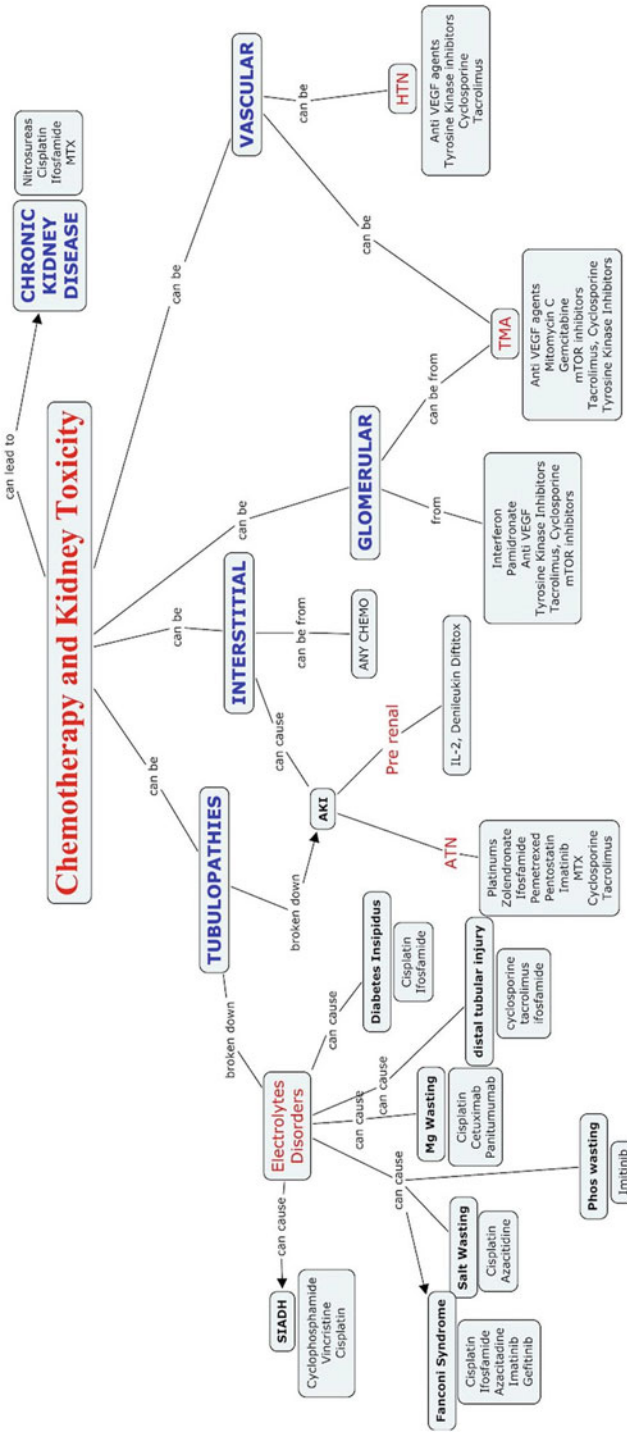

Fig. 1 Concept map of common chemotherapy associated nephrotoxicities

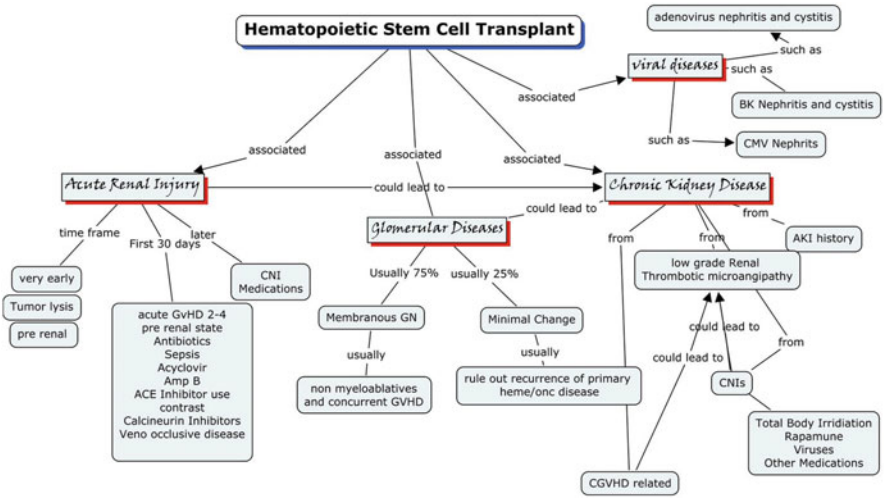

Fig. 2 Concept map of renal disease seen with hematopoietic stem cell transplant patients

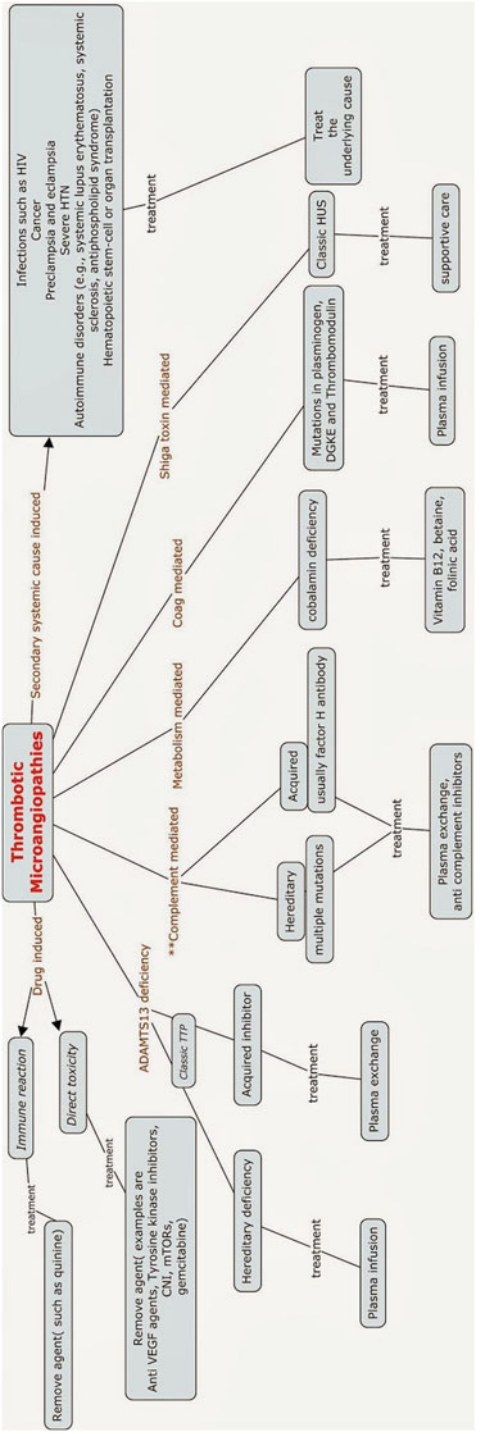

Fig. 3 Concept map of common causes of thrombotic microangiopathies (based on George J., Nester C. Syndromes of thrombotic microangiopathy. N Engl J Med 2014;371:654–666)

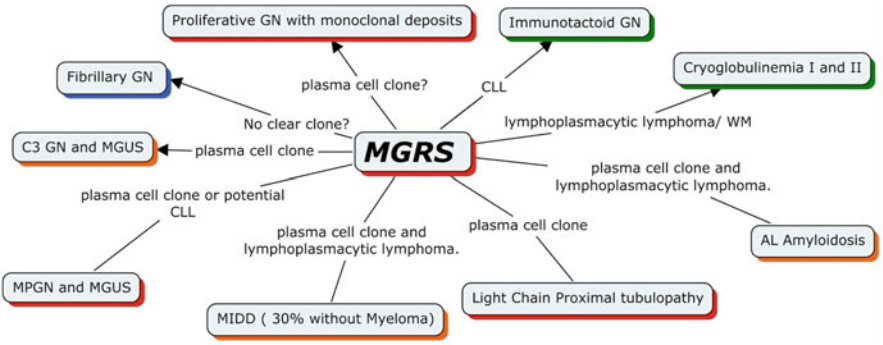

Fig. 4 Concept map of monoclonal gammopathy of renal significance (MGRS) and the clinical manifestations

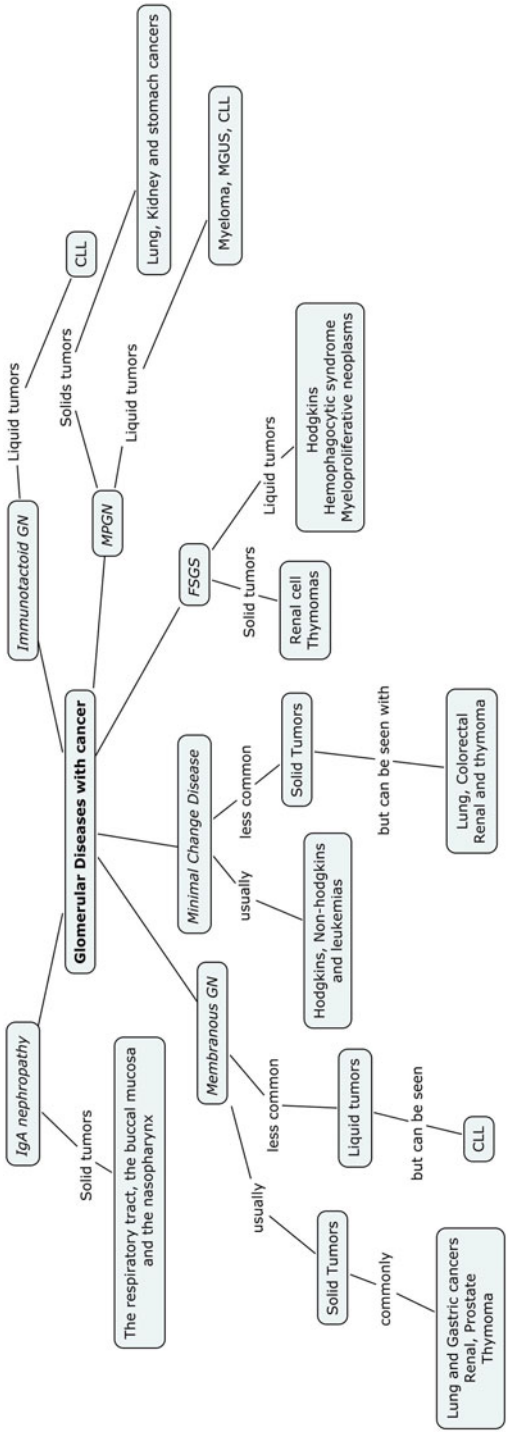

Fig. 5 Concept map of glomerular diseases seen with cancer

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