Chapter 6
Genitourinary Cancer

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Abstract Genitourinary cancers represent 12.8 % of cancer in both sexes and 21.5 % in men, accounting for 7 % of cancer deaths in both sexes and 10.5 % in men. Prostate cancer and renal cell carcinoma share the characteristic of being largely chemoresistant, with the relative exception of taxanes docetaxel and cabazitaxel, which modestly increase overall survival in late-stage prostate cancer. Prostate cancer is primarily treated by hormonal therapy, either by androgen deprivation or antiandrogens, and renal cell carcinoma is nowadays treated with agents targeting survival and angiogenesis pathways, including tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, and pazopanib; antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab; and mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus. Neither hormone therapy nor targeted therapies eradicate prostate cancer and RCC but

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rather switch them to a more chronic state. This means that these treatments are prescribed chronically for an extended period of time. In such conditions, even the least bothersome side effect may profoundly alter the quality of life of patients. Ultimately, this is a threat to compliance and then to the chronic efficacy of these treatments. In addition, many of the side effects of these drugs often overlap with common chronic illnesses such as diabetes, hypertension, hypercholesterolemia, heart failure, and osteoporosis. An exhaustive knowledge of these side effects, proper monitoring, and in-depth education of patients are key elements to secure the efficacy of these treatments.

Keywords Prostate cancer • Renal cell carcinoma • Androgen-deprivation therapy • Tyrosine kinase inhibitors • mTOR inhibitors • Side effects

Introduction

Genitourinary cancers are the leading forms of cancer and cancer deaths. Based on data from GLOBOCAN 2008, 913,000 prostate cancers, 386,000 bladder cancers, 271,000 kidney cancers, and 52,000 testis cancers have been reported, accounting for 12.8 % of cancer in both sexes and 21.5 % in men. Owing mainly to major improvements in treatment modalities, which include surgery, radiotherapy, and innovative systemic treatments, genitourinary cancers account for only 7 % of cancer deaths in both sexes and 10.5 % of cancer deaths in men.

Two genitourinary malignancies, prostate cancer and renal cell carcinoma (RCC), are characterized by a limited usage of chemotherapy, in contrast to other cancer types. Prostate cancer is primarily treated by hormone therapy, mainly androgen-deprivation therapy (ADT). Metastatic castration-resistant prostate cancer (mCRCP) was considered a lethal disease until the publication of the results of two large trials with docetaxel. More than the benefit of docetaxel itself in mCRCP, which is limited anyway, these publications have moved the treatment

of prostate cancer toward an era of multidisciplinary collaboration between specialties [1]. In contrast to many predictions, chemotherapy has never emerged as a major breakthrough treatment. It is only used in the late stages of the disease and with very modest overall survival benefit. Most studies assessing the combination of docetaxel with other classes of agent have failed to demonstrate significant benefit, and studies assessing earlier use are not conclusive. In contrast, a new twist is given to hormone therapy with the recent publication of the results with abiraterone acetate, an androgen synthesis inhibitor, and MDV3100, a novel antiandrogen. Both registration trials, conducted in a very late post-chemotherapy setting, have reported impressive benefit on overall survival. This demonstrates that prostate cancer is primarily a disease driven by the androgen receptor and that hormonal treatments, traditional and older, will remain the cornerstone strategy for years to come. Because of the particular importance of androgen-depriving therapies, a large part of this chapter will be devoted to the monitoring and prevention of side effects of hormone therapy.

Renal cell carcinoma, and especially its most frequent subtype clear cell carcinoma, is an even more peculiar disease, being both radio- and chemoresistant. Renal cell carcinoma was considered an immune-sensitive tumor as long as interferon-α (alpha)(IFN-α) and high-dose interleukin (HD-IL2) were the only available treatments. The concomitant understanding of the importance of the VHL/HIF hypoxia pathways and the development of drug-targeting angiogenesis and survival pathways has revolutionized the approach to RCC. Today, six drugs have supplanted IFN-α (alpha) and IL2, including sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab, and pazopanib. And more are yet to come. Although many of these drugs confer little or no benefit on overall survival, they have been widely accepted, and it is estimated that overall life span of patients is extended. But new modes of action have brought new types of side effects, to which physicians and patients need to become accustomed. These will be reviewed in the second part of this chapter.

Because several other chapters will address the toxicity of chemotherapy, we have chosen not to cover that topic and focus on hormone therapy of prostate cancer and targeted therapies of RCC.

Side Effects of Hormonal Treatments in Prostate Cancer

Androgen-deprivation therapy by means of surgical castration or estrogens has been the standard treatment of advanced symptomatic prostate cancer since the seminal work of Charles Huggins in the late 40s [2]. Although there is only little or no benefit on overall survival when used alone, ADT is increasingly being used in asymptomatic patients in earlier disease stages who are not candidates for local treatment [3]. ADT is also used concomitantly and adjuvant to external beam radiation therapy (EBRT), a setup that has shown the most potential to improve overall survival.

As a result many patients are receiving ADT for a prolonged period of time and will be exposed much longer to side effects. ADT is traditionally recognized through its acute and more obnoxious side effects, which include loss of libido and erectile dysfunction, hot flushes, fatigue, and psychological side effects such as emotional instability, depression, or cognitive dysfunction [4–6]. Since patients are treated earlier, more attention has been given recently to long-term toxicity, including anemia, accelerated bone loss leading eventually to osteoporosis and fragility fractures, and sarcopenic obesity, which may lead to an increased risk of cardiovascular morbidity and mortality [7].

Short-Term Adverse Events of ADT

Hot Flushes

Hot flushes are described as sudden and uncomfortable heat sensations in the face, neck, upper chest, and back, lasting from seconds up to an hour. This side effect is one of the most

common, described by up to 80 % of patients [5]. It is also one of the most bothersome side effects of ADT and may largely disrupt everyday life. Hot flushes are often triggered by stress, heat, sudden changes in body position, ingestion of warm or spicy food, or smoking [5].

Management of hot flushes includes informing patients to avoid triggering situations. If hot flushes are very bothersome for patients, medical therapy can be considered. Hormonal agents such as megestrol acetate, medroxyprogesterone acetate, cyproterone acetate, and low-dose diethylstilbestrol are very popular to treat bothersome hot flushes [4–6, 8]. Selective serotonin reuptake inhibitors (SSRIs) (i.e., venlafaxine or citalopram), (alpha) α-adrenergic inhibitors (i.e., clonidine), and GABA analogue gabapentin are alternatives to hormonal agents, although their efficacy is usually lower [9–11]. Acupuncture and phytotherapy, especially sage extracts, can also be recommended to patients, despite lack of definitive robust scientific evidence [12, 13].

Sexual Dysfunction

The negative impact of ADT on libido and sexual function is well known, including decrease of sexual desire and impotence [14]. Patients and their partners should be informed about this, as it can cause anxiety for both. It should be stressed, however, that the extent of sexual dysfunction vary widely from one patient to another and that a satisfying sexual and affective life is possible under ADT. From a historic review of the social and intellectual performances of eunuchs, Aucoin and Wassersug suggested that given the right cultural setting and individual motivation, ADT may actually enhance, rather than hinder, both social and sexual performance [15]. Traditional treatments of erectile dysfunction can be recommended in ADT-treated patients, including intra-cavernous injections of prostaglandins and/or phospodiesterase-5 inhibitors. Physicians should always remember that ADT induces first a libido problem and that patient and partner counseling may prove as effective as medications.

Fatigue

Fatigue is one of the most common side effects of ADT. Although fatigue is very difficult to fight, lifestyle changes and especially physical exercise may help to alleviate fatigue and improve quality of life. A systematic review on 34 trials examining the effectiveness of physical exercise in improving the physical functioning and psychological well-being of prostate cancer patients during and after treatment suggested that cancer patients may indeed benefit from physical exercise [16]. The Fresh Start trial has randomized 543 subjects with newly diagnosed locoregional breast or prostate cancer to receive a 10-month-specific program promoting diet changes and physical exercise or nonspecific information. Although subjects in both arms significantly improved their lifestyle behavior, significantly greater improvement was observed in subjects receiving the diet- and exercise-specific information [17]. Physicians should try to convince patients to adopt a healthier lifestyle including a healthy diet and physical exercise. Fatigue may be further aggravated by the sarcopenia (loss of skeletal muscle mass) resulting from ADT, which directly impacts on muscle strength and reduces physical activity [18].

Psychological Side Effects

Androgen-deprivation therapy may have psychological side effects such as reduced cognitive function (e.g., reduced concentration and memory problems) and emotional instability or even depression [5, 6]. Patients and relatives should be informed about the likelihood of emotional changes and how to identify early signs of depression or decreased cognitive function in order to ensure rapid referral to a specialist. It is also important to explain these side effects to the patient's family so that they understand their nature and origin and can help the patient adapt to them. Depression can be severe, so that an increased risk of suicide in the months following diagnosis of advanced prostate cancer has been reported, probably as a mixed effect of the cancer diagnosis and the initiation of ADT [19].

Adrenal Insufficiency

Abiraterone acetate is a newly developed and approved androgen synthesis inhibitor that increases overall survival in mCRPC [20]. Abiraterone's mode of action is different from LHRH agonists and antagonists since it targets CYP17, a key enzyme that mediates androgen synthesis in the testes and adrenal glands. Abiraterone not only inhibits the synthesis of androgens but also suppresses cortisol synthesis [21]. This induces a reciprocal increase in pituitary adrenocorticotrophic hormone (ACTH) and therefore an elevation of corticosterone. This may lead to fluid retention, hypokalemia, and hypertension. To prevent these side effects, abiraterone must be combined with corticosteroids, prednisolone, prednisone, or dexamethasone, or mineralocorticoids such as eplerenone.

Long-Term Adverse Events of ADT

Anemia

In at least 90 % of ADT patients, hemoglobin level will drop on average by 10 % [22]. Anemia associated with ADT is usually normocytic, normochromic, and due to the lack of androgen stimulation of erythroid precursors and a decrease in erythropoietin production. Anemia worsens fatigue [5]. Physicians should closely monitor hemoglobin levels in patients treated with ADT. Anemia may be aggravated by extensive invasion of the bone marrow, which occurs frequently in mCRPC patients. Subcutaneous administration of recombinant human erythropoietin and/or transfusion may be required in severe cases.

Metabolic and Cardiovascular Side Effects

Physiopathology of Cardiovascular Toxicity in ADT-Treated Patients

Androgen-deprivation therapy causes changes in the patient's body mass and composition [5, 18]. Suppression of testosterone

level causes a situation known as sarcopenic obesity, combining muscular atrophy and an increase in fatty tissue [23,24]. By creating an imbalance between lean and fatty mass, sarcopenic obesity induces many of the phenotypic features of the metabolic syndrome, such as increased subcutaneous fat, increased total and high-density lipoprotein (HDL) cholesterol, and increased adiponectin levels [25,26]. The main cause of these metabolic changes is an increased peripheral resistance to insulin, leading to type 2 diabetes [27]. These metabolic changes may be facilitated by reduced physical activity resulting from fatigue and depression.

Impact of Metabolic Changes on Cardiovascular Events

In a observational study on 37,443 men, Keating et al. reported that ADT significantly increases the risk of diabetes (hazard ratio [HR] 1.28; 95 % CI 1.19–1.38), coronary heart disease (CHD) (HR 1.19; 95 % CI 1.10–1.28), myocardial infarction (MI) (HR 1.28; 95 % CI 1.08–1.52), sudden death (HR 1.35; 95 % CI 1.18–1.54), and stroke (HR 1.22; 95 % CI 1.10–1.36). Combined androgen blockade and orchiectomy further increased all risks; in contrast, pure oral antiandrogen monotherapy had no detectable impact [28]. Another study on 73,196 men from Surveillance, Epidemiology, and End Results (SEER) Medicare data ($n = 73,196$) has confirmed these data. GnRH agonists were associated with increased risk of diabetes (HR 1.44; $p < 0.001$), CHD (HR 1.16; $p < 0.001$), MI (HR 1.11; $p = 0.03$), and sudden cardiac death (HR 1.16; $p = 0.004$) [29]. Saigal et al. have examined the risk of cardiovascular morbidity in 22,816 men ≥65 years with newly diagnosed prostate cancer on ADT also using the SEER Medicare data. They found that men who received ADT had a 20 % higher risk of cardiovascular morbidity compared with similar men who did not receive ADT (HR 1.20; $p < 0.05$) [30].

Does ADT Increase the Risk of Death from Cardiovascular Disease?

Three retrospective cohort studies have suggested a significant increase in the risk of cardiovascular-related mortality from ADT, with HR of respectively 1.16, 1.35, and 2.6 [28, 31, 32].

The study by Tsai et al. included 4,892 patients from the Cancer of the Prostatic Urologic Research Endeavor (CAPSURE) database and suggested that ADT increases cardiovascular mortality in the subset of men undergoing radical prostatectomy for localized prostate cancer (HR = 2.6; $p = 0.002$) but not in a subset of men treated with external beam radiation therapy (EBRT) [32].

Not all published studies, however, have reported a relationship between ADT and greater risk of cardiovascular death. Secondary analyses of four randomized controlled studies from the Radiation Therapy Oncology Group (RTOG) or European Organization for Research and Treatment of Cancer (EORTC) have found no association between neo-adjuvant or adjuvant ADT and cardiovascular-related mortality [33–36]. It has to be noted that these studies were not primarily designed to specifically assess cardiovascular mortality. A recent EORTC randomized study comparing EBRT plus 6 months or 3 years of ADT in patients with locally advanced prostate cancer showed no significant difference in the incidence of fatal cardiac events at 5-year follow-up in patients receiving ADT of longer duration (4.0 % vs. 3.0 %, respectively) [37].

Whether there is a causal relationship between ADT and cardiovascular morbidity and mortality remains controversial and continues to be studied. However, at this point in time, experts believe that it is reasonable to state that there may be an association between ADT and cardiovascular events and death because of the adverse effect of ADT on risk factors for cardiovascular disease [38]. On October 20, 2010, the US Food and Drug Administration (FDA) notified the manufacturers of the GnRH agonists of the need to add new safety information to the warnings and precautions section of the drug labels [39]. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer.

Risk Factors for Cardiovascular Events

The risk of cardiovascular disease is not correlated with the duration of hormone therapy. Previous longitudinal studies

have shown that 6 months of ADT was enough to induce metabolic changes causing the increase in cardiovascular risk [25, 26]. In the study reported by Keating et al., the increased cardiovascular risk was observed within the initial 12 months of ADT [28]. Age seems to be an important predictive factor. In the epidemiological survey by Tsai et al., the impact of ADT on cardiovascular risk was much higher for men >65 years old than for younger men [32]. The 5-year cumulative incidence of cardiovascular mortality was 5.5 % for patients ≥65 years who received ADT and 2 % for non-ADT controls. For younger patients, the 5-year cumulative incidence of CV mortality was 3.6 % for those who received ADT and 2 % in those not treated with ADT.

In addition to age, preexisting comorbidities are very important. Nanda et al. reported the results of a retrospective study including 5,077 men with localized or locally advanced prostate cancer who were treated by EBRT with or without a median of 4 months of neo-adjuvant ADT [40]. They found that the use of neo-adjuvant ADT was associated with an increased risk of all-cause mortality among men with a history of coronary artery disease (CAD)-induced congestive heart failure (CHF) or myocardial infarction (MI) but not among men with no comorbidity or a single CAD risk factor. In the subgroup of patients with CAD-induced CHF or MI, 26.3 % deaths were reported in ADT-treated patients and 11.2 % deaths in non-ADT-treated controls (HR 1.96; 95 % CI 1.04–3.71; $p = 0.04$) [40]. D'Amico et al. have analyzed post-hoc pooled data on 1,372 patients from three randomized trials of EBRT with or without ADT for localized prostate cancer [41]. They found a shorter time to fatal MI in men aged ≥65 years who received 6 months of ADT compared with men in this age group with no ADT use ($p = 0.017$). Additional evidence to support this result is needed.

Monitoring and Prevention of Cardiovascular Events

Physicians should carefully monitor the metabolic and cardiovascular parameters of patients treated with ADT, including blood pressure, serum lipid level, and hemoglobin and fasting

serum glucose levels [4–6, 42, 43]. Physicians should encourage patients to adopt a healthier lifestyle, including an appropriate low-fat diet and regular physical exercise. Nobes et al. have investigated the effects of metformin and lifestyle changes on the development of ADT-related metabolic changes [44]. In total, 40 men scheduled to receive 6 months ADT have been randomized between standard care and 6 months of metformin, a low glycemic index diet, and an exercise program. After 6 months, significant improvements in abdominal perimeter, weight, body mass index, and systolic blood pressure were seen in the intervention arm compared to controls.

Resistance training is a form of strength training in which each effort is performed against a specific opposing force generated by resistance. Resistance exercise is used to develop the strength and size of skeletal muscles. Properly performed, resistance training can provide significant functional benefits and improvement in overall health and well-being. A study conducted by Galvão et al. demonstrated that 20 weeks of progressive resistance exercise performed in a rehabilitation clinic increased muscle strength and endurance and preserved whole-body lean mass with no change in fat mass [45]. Segal et al. demonstrated that men assigned to resistance exercise had less interference from fatigue on activities of daily living and a better quality of life than untrained men [46]. The same group demonstrated that a combination of both resistance and aerobic exercise mitigates fatigue in patients treated by EBRT with or without ADT [47]. Resistance exercise generated longer-term improvements and additional benefits for quality of life, strength, triglyceride levels, and body fat. Baumann et al. have performed a meta-analysis of 25 randomized controlled trials regarding physical activities in prostate cancer patients, including 21 investigating exercise interventions during the phase of medical treatment and 4 during the aftercare [48]. This meta-analysis suggests that incontinence, fitness, fatigue, body constitution, and also quality of life can be improved by clinical exercise in patients during and after prostate cancer treatment. Only four studies, all conducted during medical treatment, reached the level “1b” and concluded that “supervised” exercise is more effective than “non-supervised” exercise.

Table 6.1 Prospective studies measuring bone loss associated with ADT

Study	Treatment	BMD decrease at 12 months (%)
Eriksson et al. (1995) [49]	Orchiectomy	Hip: 9.6 Radius: 4.5
Maillefert et al. (1999) [53]	GnRH agonist	Hip: 3.9 Lumbar spine: 4.6
Daniell (1997) [54]	Orchiectomy GnRH agonist	Hip: 2.4
Daniell et al. (2000) [55]	GnRH agonist	Hip: 0.6 Lumbar spine: 2.3
Higano et al. (2004) [56]	LHRH agonist + antiandrogen	Hip: 2.7 Lumbar spine: 4.7
Mittan et al. (2002) [57]	GnRH agonist	Hip: 3.3 Radius: 5.3

Skeletal Complications of ADT

Cancer Treatment–Induced Bone Loss (CTIBL) and ADT

The association between surgical castration and accelerated bone loss, and the fact that administration of estrogens does not prevent this, was first described more than 15 years ago [49]. Longitudinal studies suggest that bone loss accelerates after the age of 70 years in men, probably related to the decrease in testosterone and estradiol levels observed in aging males [50–52]. Prospective studies measuring bone loss associated with ADT have been performed for more than 10 years and have consistently observed a significant deterioration of bone mineral density (BMD) over time (Table 6.1). Substantial bone loss begins very early in the course of treatment with ADT. Mittan et al. reported that, in comparison to 15 age-matched untreated controls, the concentration of urinary N-telopeptide (uNtx, a biomarker for bone resorption) in

patients receiving ADT was significantly higher after 6 months of treatment, indicative of early bone loss [57].

ADT and Fragility Fractures

Several epidemiologic studies have confirmed that CTIBL increases the risk of fragility fractures (Table 6.2), which in turn may decrease survival. Several risk factors for fragility fractures have been identified, the most important being the duration of ADT. In a Cox proportional hazards analysis of Shahinian's epidemiologic survey, there was a statistically significant relation between the duration of ADT and the subsequent risk of fracture [58]. The relative risk of any fracture was 1.07 for patients receiving 1–4 doses of trimonthly GnRH agonists, 1.22 for 5–8 doses, 1.45 for ≥9 doses, and 1.54 for patients treated by orchiectomy. In addition to ADT duration, other risk factors for fracture include race and low body mass index (<25 kg/m^2) [61]. In Alibhai's survey, independent predictors of fragility and any fracture were increasing age, prior bone thinning medications, chronic kidney disease, prior dementia, prior fragility fracture, and prior osteoporosis diagnosis or treatment ($p < 0.05$) [60].

Monitoring and Prevention of CTIBL in ADT-Treated Patients

Since bone loss occurs rapidly during ADT, physicians should inform patients and take all appropriate measures to monitor and minimize bone loss as early as possible during treatment. Early diagnosis of bone loss and treatment to improve bone health are important to protect patients from fractures, which are difficult to heal in mature adults.

Dual-energy x-ray absorptiometry (DXA) should be used to monitor spine, hip, or total body BMD. The spine is the preferred site of densitometry for serial measurement of bone mass to monitor changes in BMD [62]. When spine measurements are technically invalid, especially in the presence of bone metastases, total hip BMD should be assessed [62]. Status of bone health is typically based on the T-score measurement that compares a patient's BMD to that of a 30-year-old healthy person (baseline).

Table 6.2 Reported fracture risk in patients receiving hormone therapy[a]

			Fracture risk (%)					
			All sites		Hip		Hospitalization	
Study	Patients *n*.	ADT duration (years)	ADT	No ADT	ADT	No ADT	ADT	No ADT
Shahinian et al. (2005) [58]	50,613	1–5	19.6	12.6	4.06	2.06	5.19	2.37
Smith et al. (2005) [59]	11,661	>12	7.88*	6.51*	1.26*	0.98*		
Alibhai et al. (2010) [60]	19,079	6.7	17.2	12.7	2.6	2	8	5.7

Abbreviation: *ADT* androgen-deprivation therapy

*$p < 0.05$

[a]Rate (%) per person per year

Table 6.3 Risk ratio for hip fracture according to risk factors adjusted for age and bone mineral density in men and women

Risk factor for hip fracture	Adjusted risk ratio (95 % CI)
Low or high BMI	
20 vs. 25	1.42 (1.23–1.65)
30 vs. 25	1.00 (0.82–1.21)
Prior fracture at >50 years of age	1.62 (1.30–2.01)
Parental history of hip fracture	2.28 (1.48–3.51)
Current smoking	1.60 (1.27–2.02)
Use of systemic corticosteroids for >3 months	2.25 (1.60–3.15)
Excessive alcohol use	1.70 (1.20–2.42)
Rheumatoid arthritis	1.73 (0.94–3.20)
Low testosterone	
Hip fracture	1.88 (1.24–2.82)
Other non-vertebral fracture	1.32 (1.03–1.68)

Adapted from [63]

For every standard deviation below this baseline, the relative risk of fracture increases from 1.5- to 2.5-fold. A patient with a T-score above –1 is considered to have healthy bone, a score of –1 to –2.5 is osteopenic, below –2.5 is osteoporotic, and a score below –2.5 with any associated fracture is considered severely osteoporotic [63]. A patient with a T-score below –2.5 has approximately an 11-fold increase in the risk of developing a fracture than a patient with normal BMD [64]. There is no uniform recommendation about when to perform the first DXA scan in patients treated with ADT. The European Association of Urology (EAU) guidelines recommend performing the first DXA scan before long-term ADT is initiated, but there is no cut-off duration defining long-term ADT and no recommendation on scheduling of subsequent DXA scans [65]. Similarly, physicians should be attentive to the presence of additional risk factors, as highlighted by Ebeling (Table 6.3) [63].

In terms of prevention, patients should be encouraged to make specific lifestyle changes: cessation of smoking, moderate alcohol and caffeine consumption, and regular weight-bearing exercises [5]. Patients should also be encouraged to consume a healthy diet of foods and beverages containing calcium (dairy) and vitamin D (fatty fish). The recommended daily intake of calcium should be 1,200–1,500 mg, and serum levels of hydroxyvitamin D should be maintained at ≥30 ng/mL [63, 66]. If necessary, supplementation with cholecalciferol at doses of 800–2,000 IU/day should be given. A systematic review of around 64,000 men and women showed that a daily intake of calcium (≥1,200 mg) or calcium with vitamin D (≥800 IU daily) reduced the frequency of osteoporotic fractures by 12 % in men and women aged ≥50 years [67]. Physical exercise is also a very important part of preventing bone loss. Resistance exercise is particularly favorable for maintaining or improving bone mass and architecture while also being safe for older people [68].

Pharmacologic Prevention and Treatment of CTIBL in ADT-Treated Patients

The EAU guidelines acknowledge that patients with osteoporosis or severe osteoporosis should be treated with a bisphosphonates even though these agents are not approved for this indication [65]. The last posted version of the National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer advises pharmacologic treatment for men when the 10-year probability of hip fracture is ≥3 % or major osteoporosis-related fracture is ≥20 % [69]. The NCCN guidelines recommend assessing fracture risk using the FRAX algorithm (www.shef.ac.uk/FRAX/index.htm) by considering CTIBL as "secondary osteoporosis." The FRAX algorithm, however, has never been prospectively validated on a cohort of ADT-treated men.

Bisphosphonates

Pamidronate (at a dose of 60 mg IV every 12 weeks) was the first bisphosphonate to be studied for the prevention of CTIBL in prostate cancer in a randomized controlled trial [70].

After 1 year, BMD decreased by 3.3 % at the lumbar spine ($p < 0.001$) and by 1.8 % at the hip ($p > 0.005$) in untreated patients. No change in BMD occurred in patients receiving pamidronate. Fracture rate was not reported.

Two double-blind, randomized, placebo-controlled clinical trials have evaluated the effect of zoledronic acid on BMD in ADT-treated patients with non-metastatic prostate cancer. In the first trial, patients received zoledronic acid, 4 mg, or placebo IV every 3 months for 1 year [71]. Mean lumbar spine BMD increased by 5.6 % in men receiving the bisphosphonate ($n = 42$) but decreased by 2.2 % in the placebo group ($n = 37$) ($p < 0.001$). The second trial evaluated the efficacy of a 4-mg annual zoledronic acid infusion [72]. Mean BMD of the lumbar spine increased by 4.0 % with the bisphosphonate and decreased by 3.1 % with the placebo ($p < 0.001$); the total hip BMD increased by 0.7 % with the bisphosphonate and decreased by 1.9 % with placebo and ($p = 0.004$). To date, none of the studies with zoledronic acid have demonstrated a benefit on fractures.

The oral bisphosphonate, alendronate, at the weekly dosage of 70 mg, has also been tested in 44 men, of whom 39 % had osteoporosis and 52 % had low BMD at baseline [73]. In men treated with alendronate, BMD increased over 1 year by 3.7 % ($p < 0.001$) at the spine and 1.6 % ($p = 0.008$) at the femoral neck. Among men in the placebo group, there were reductions in BMD of 1.4 % ($p = 0.045$) at the spine and 0.7 % ($p = 0.081$) at the femoral neck.

Low-Dose Denosumab

Denosumab is a fully human monoclonal antibody that specifically inhibits RANKL, a critical mediator of osteoblast-to-osteoclast crosstalk. Injection of denosumab results in a prolonged inhibition of bone remodeling in postmenopausal women [74]. The prospective, randomized, placebo-controlled hormonal ablation therapy (HALT) study has investigated the benefit of denosumab in the prevention of CTIBL and fractures in 1,400 patients with non-metastatic prostate cancer receiving

ADT [75]. To be eligible for the study, patients had to be 70 years of age or older or alternatively had either a low BMD (T-score at the lumbar spine, total hip, or femoral neck of less than −1.0) at baseline or history of an osteoporotic fracture. Denosumab was administered every 6 months subcutaneously at a dose of 60 mg. After 24 months, BMD at the lumbar spine had increased by 5.6 % in the denosumab group as compared with a loss of 1.0 % in the placebo group ($p < 0.001$). Patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5 % vs. 3.9 % with placebo) (relative risk: 0.38; 95 % CI 0.19–0.78; $p = 0.006$). The rates of adverse events were similar between the two groups. Recently, denosumab was approved for the management of bone loss associated with treatment of prostate cancer [76].

Checklist for Monitoring Patients Receiving ADT

Before initiating treatment:

- Inform the patient about the occurrence of hot flushes and provide lifestyle recommendations to avoid excessive triggering.
- Inform the patient and his partner about libido, mood, and cognitive changes.
- Encourage maintaining and even increasing social activities and networking, possibly referring to patient support groups.
- Inform in due time the patient's general practitioner, cardiologist, and endocrinologist about initiation of ADT. Advise the patient to schedule a follow-up visit with these specialists within 6 months.
- Provide dietetic counseling and recommend resistance exercise. This will be done optimally by referring the patient to a dietician and physical therapist or by administrating a specifically designed coaching program.
- Search for risk factors of bone loss, and perform an immediate DXA scan, if they are present.

During treatment:

- In addition to PSA and testosterone measurements and imaging studies that are required for oncologic follow-up, it is recommended to measure weight and abdominal perimeter (or preferably body fatty tissue content by impedance technique), blood pressure, and dose hemoglobin, fasting cholesterol (total and HDL), triglyceride, and glucose levels. In case of abnormalities, refer the patient to a specialist.
- Advise a DXA scan after 1–2 years of ADT.

Side Effects of Targeted Therapies for Renal Cell Carcinoma

The treatment of RCC has been revolutionized by the development in the early 2000s of six therapies targeting the VHL/HIF pathways. These belong to three different classes of drug: the tyrosine kinase inhibitors (TKIs), including sunitinib and pazopanib, and also the multikinase inhibitor sorafenib; the antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab; and the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus [77–87]. Although most of these drugs have individually demonstrated little benefit on overall survival, the prognosis for advanced RCC is shifting progressively toward that of a chronic treatable disease (Table 6.4). A result of this is that patients are nowadays treated for increasingly longer periods of time with these agents.

Because these drugs belong to new therapeutic classes, they cause class side effects that are new for physicians and have raised new challenges related to their management. Most of these side effects are not life-threatening but can severely hamper the quality of life of patients on the long run. Because it is very important to secure long-term compliance to oral drugs, it is critical that side effects are managed preemptively and that patients are correctly informed and educated

Table 6.4 Summary of benefit of new targeted agents used in RCC

Agent	*N*	ORR (%)	Median PFS (months)	Median OS (months)
First-line therapy				
Sunitinib vs. IFN-α [83, 84]	750	47 vs. 12 $p<0.001$	11.0 vs. 5 $p<0.001$	26.4 vs. 21.8 $p=0.051$
Temsirolimus vs. IFN-α (alpha) [81]	626	8.6 vs. 4.8 NS	5.5 vs. 3.1 $p<0.0001$	10.9 vs. 7.1 $p=0.008$
Bevacizumab + IFN-α(alpha) vs. IFN-α (alpha) [79]	649	31 vs. 13 $p=0.0001$	10.2 vs. 5.4 $p=0.0001$	IFN-α(alpha) 19.8 B/IFN-α (alpha) NR $p=0.0267$
Bevacizumab + IFN-α (alpha) vs. IFN-α (alpha) [86]	732	26 vs. 13 $p<0.0001$	8.5 vs. 5.2 $p<0.0001$	NR
Sorafenib vs. IFN-α (alpha) [80]	189	5 vs. 9	5.7 vs. 5.6 $p=0.504$	NR

Pazopanib vs. placebo [87]	435	30 vs. 3 $p<0.001$	9.2 vs. 4.2 $p<0.001$	21.1 vs. 18.7 $p=0.02$
Second-line therapy				
Sorafenib vs. placebo [77]	750	10 vs. 2 $p<0.001$	5.5 vs. 2.8 $p<0.001$	17.8 vs. 15.2
Everolimus vs. placebo [82]	410	5 vs. 0 NS	4.9 vs. 1.9 $p<0.0001$	14.8 vs. 14.4
Axitinib vs. sorafenib [85]	723		6.7 vs. 4.7 $p<0.001$	

about the preventive measures. There are many generic side effects associated with TKIs and mTOR inhibitors, including fatigue, hypertension, and diarrhea. In addition, there are several agent-specific side effects: proteinuria, with bevacizumab plus IFN; hypothyroidism, with sunitinib; hand-foot skin reaction (HFSR), most often seen with sorafenib; hepatotoxicity, most often seen with pazopanib; and hyperlipidemia, most often seen with the mTOR inhibitors [77–79, 87–93]. These side effects and their respective frequencies are summarized in Table 6.5.

The impact of side effects can be greatly limited if the patient is well informed and one encourages activating preventive measures. Even mild side effects may have a great impact on a patient's quality of life and require temporary dose reduction or treatment discontinuation. Physicians should be aware of comorbidities such as diabetes and hypertension that may also increase the risk of certain side effects. To ensure early detection and optimal management of side effects and to maximize patient benefits and compliance, it is important that the physician be aware of the range of manageable side effects associated with each agent and that this information is effectively communicated to the patients.

Life-Threatening Side Effects

In addition to these frequent side effects, potentially life-threatening or lethal adverse events have been reported in the Summary of Product Characteristics of the European Medicines Agency.

Sorafenib has been reported to cause reversible posterior leukoencephalopathy, hypertensive crisis, cardiac ischemia and myocardial infarction, gastrointestinal perforation, and hemorrhage [88]. Pre-neoplasic skin lesions such as actinic keratosis and keratoacanthomas, but also squamous cell carcinoma, have been reported.

Sunitinib has been reported to cause life-threatening hematologic, cardiovascular, and venous thromboembolic events, pancreatic and hepatobiliary complications, gastrointestinal perforation, and hemorrhage [89].

Table 6.5 Most commonly reported side effects in Summary of Product Characteristics European Medicines Agency for sorafenib [88], sunitinib [89], pazopanib [93], bevacizumab [91], temsirolimus [90], and everolimus [92]

Side effect	TKIs	Anti-VEGF			mTOR inhibitor	
	Sorafenib	Sunitinib	Pazopanib	Bevacizumab	Temsirolimus	Everolimus
Gastrointestinal disorders						
Constipation	C	VC		VC		
Diarrhea	VC	VC	VC	VC	VC	VC
Dyspepsia	C	VC				
Dry mouth	C	VC				C
Flatulence		C	C		C	
Glossodynia		VC				C
Nausea		VC	VC	VC	VC	VC
Oral pain		C			VC	C
Stomatitis	C	VC	C	VC	VC	VC
Vomiting	VC	VC	VC	VC	VC	VC
Abdominal pain			VC	C	C	

TABLE 6.5 (continued)

Side effect	TKIs	Anti-VEGF			mTOR inhibitor	
	Sorafenib	Sunitinib	Pazopanib	Bevacizumab	Temsirolimus	Everolimus
Gastrointestinal perforation	UC			C	UC	
Dermatologic side effects						
Acne	C	C			VC	C
Alopecia	VC	C	C			C
Dry skin	C	VC		VC		VC
Erythema	VC	C	C			C
Hair color changes		VC	VC			
HFSR	VC	VC		C		C
Nail disorder	C	C			VC	VC
Pruritus	VC	C	C		VC	
Rash	VC	VC	C		VC	VC
Skin discoloration		VC		VC		
Bacterial and viral infections	UC		UC	C	VC	VC

Respiratory disorders						
Cough	C	C	C		VC	VC
Dyspnea		C		C	VC	VC
Epistaxis		VC	C	C	VC	VC
Pneumonitis	UC	C			C	VC
Pleural effusion					C	
Cardiovascular disorders						
Ejection fraction decreased	C	C	UC			
Hemorrhage	VC				VC	VC
Hypertension	C	VC	UC	VC	C	VC
Deep vein thrombosis				C		
Thromboembolism				C	C	C
Supraventricular tachycardia				C		
Pulmonary embolism			UC	C	C	

(continued)

TABLE 6.5 (continued)

Side effect	TKIs	Anti-VEGF			mTOR inhibitor	
	Sorafenib	Sunitinib	Pazopanib	Bevacizumab	Temsirolimus	Everolimus
Metabolic disorders						
Anorexia	C	VC	C	VC	VC	VC
Hypokalemia					VC	C
Hyperglycemia					VC	VC
Hypercholesterolemia					VC	VC
Hyperlipidemia					VC	VC
Hypophosphatemia	VC		C		VC	C
Hematologic disorders						
Neutropenia	C	VC	C	VC	C	C
Thrombocytopenia	C	VC	C	VC	VC	VC
Anemia	C	VC		C	VC	VC
Leucopenia	C	C	C	VC	C	C
Lymphopenia	VC	C			C	C
Laboratory abnormalities						
Creatinine increase	C	C			VC	C

Increase liver enzyme	UC	UC	VC		C	C
Proteinuria		UC	C	VC	C	C
Central nervous system disorders						
Headache	VC	VC	C	C	VC	
Peripheral sensory neuropathy	C	C	UC	VC		
Depression	C	C		C	C	
Intracerebral bleeding					C	
Taste disturbance		VC	VC	VC	VC	
Musculoskeletal disorders						
Arthralgia–myalgia	C	VC	C	VC	VC	C
Ophthalmologic side effects						
Lacrimation increased		C		VC		
Eyelid edema		C		VC		VC
Conjunctivitis				C		VC
Eyelash decoloration			UC			

(continued)

Table 6.5 (continued)

Side effect	TKIs	Anti-VEGF			mTOR inhibitor	
	Sorafenib	Sunitinib	Pazopanib	Bevacizumab	Temsirolimus	Everolimus
Others						
Allergic reactions	UC	UC		C		
Fatigue	VC	VC	VC	VC	VC	VC
Hypothyroidism	UC	C	C			
Hyperthyroidism	UC	UC		VC		
Insomnia		C		VC	VC	VC
Mucosal inflammation	VC	VC	C	C		
Edema		VC	C		VC	VC
Pyrexia					VC	VC

Adapted from [94]

Frequencies are reported as very common (VC; ≥1/10 patients), common (C; ≥1/100 to <1/10 patients), or uncommon (UC; ≥1/1,000 to <1/100 patients). Cases are empty if the incidence of the side effect is not reported in Eu SmPC or cannot be estimated from the data available

The association of *bevacizumab + IFN-α* has been reported to cause hypertensive encephalopathy, cardiac failure, thromboembolic events, gastrointestinal perforation, and hemorrhage [91].

Pazopanib has been reported to cause gastrointestinal perforation and gastrointestinal fistula, arterial thrombotic events, hemorrhage, and severe hepatotoxicity [93].

Temsirolimus has been reported to cause hypersensitivity/infusion reactions, intracerebral bleeding, bowel perforation, pericardial effusion, pneumonitis, renal failure, and delay wound healing [90].

Everolimus has been reported to cause noninfectious pneumonitis and infections [92].

Prevention and Management of Most Common Side Effects

Dermatologic Side Effects

Early recognition of dermatologic complications is critical, and patients should be taught to report the development of any new skin lesions.

Rash and *hand-foot skin reaction* (*HFSR*) are among the most troubling and common side effect of TKIs. Hand-foot skin reaction occurs in 30–60 % of patients receiving sorafenib and 15–20 % of patients treated with sunitinib. Hand-foot skin reaction appears usually after 2–4 weeks of treatment. The onset and severity of HFSR appear to be dose-dependent and often disappear rapidly upon treatment discontinuation. The physiopathology of HFSR is unclear, although it is relatively infrequent with pazopanib. The severity of HFSR can range from minimal skin changes (grade 1) to painful ulcerative dermatitis (grade 3) and often results in dose reduction.

There are no dedicated studies defining the degree of benefit of commonly reported measures for the management of HFSR. Preventive measures for HFSR include removal of any existing hyperkeratosic areas and calluses beforehand [95]. It is important that pressure areas are protected and treated with moisturizing creams or ointments. During treatment,

care should be taken to reduce exposure of the hands and feet to hot water and to avoid constrictive footwear, friction, and trauma arising from exercise. Shoes with padded insoles (and possibly also gloves) can be worn. There may be benefit in sparingly applying moisturizing cream to the hands and feet and educating patients on the first signs of HFSR [96]. Wearing soft and not constrictive shoes and even gloves is recommended. Once it is present, HSFR should be managed with topical application of corticoids-containing cream. Dose reduction, interruption, and event discontinuation may be required for grade 2/3 toxicities.

Management strategies for rash require first differentiating nonserious rash, which is usually moderate and not associated with systemic symptoms, from more severe hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome or Stevens–Johnson syndrome. These are usually associated with mucosal involvement, bullous lesions, and systemic and biological signs. Meticulous skin care, moisturizing cream, and urea-containing lotion are key preventive and therapeutic measures. They require immediate drug discontinuation and specialized dermatologic support.

Infections

Everolimus and temsirolimus have dose-dependent immunosuppressive properties and can therefore predispose patients to infections. In the temsirolimus phase III study, infections were reported in 27 % of patients (grade 3/4 in 5 %) receiving temsirolimus versus 14 % in the control arm [81]. In the everolimus phase III study, infections were reported in 13 % of patients (grade 3/4 in 4 %) versus 2 % (grade 3/4 in 0 %) in the control arm [82]. Physicians should be aware of this increased risk and should ensure that any preexisting infections are adequately treated before initiation of mTOR inhibitors. It is particularly important that patients with pulmonary infiltrates or pulmonary symptoms, which are also frequent with mTOR inhibitors, are rigorously assessed for signs of infection, owing to the potential overlap between pulmonary infections and noninfectious pneumonitis.

Gastrointestinal Side Effects

Diarrhea

Diarrhea is one of the most common side effects of anticancer therapy. It is not only inconvenient but also potentially life-threatening if not sufficiently managed. There are a number of published clinical guidelines for the management of diarrhea in cancer patients that apply also to targeted therapies in RCC [97]. Patients must be advised to avoid foods that may aggravate diarrhea and favor foods that increase the consistency of stools. In case of persistent diarrhea, it is important to maintain abundant liquid and salt intake by using, for example, a WHO solution containing 30 mL (6 level teaspoon) of sugar and 2.5 mL (1/2 level teaspoon) of salt, dissolved into 1 L of water. Loperamide is widely prescribed for anticancer therapy-related diarrhea. For grade 3 or 4 diarrhea, dose adjustments or even discontinuation may be required.

Oral or Upper Gastrointestinal Complications

Oral and upper tract gastrointestinal complications of targeted therapies are very common and include mucositis, stomatitis, dry mouth, and taste loss or disturbance [88–93]. Mucositis is characterized by painful inflammation and ulceration of the mucous membranes lining the digestive tract, whereas stomatitis more specifically refers to painful inflammation of the mucous lining of the mouth. A meta-analysis by Worthington et al. has evaluated the effectiveness of prophylactic agents for preventing stomatitis in patients receiving chemotherapy [98]. Results from their analysis suggest that amifostine, a Chinese medicine (that involved mixtures of 5 or 11 herbs, including honeysuckle flower, licorice root, and magnolia bark), hydrolytic enzymes (pepsin, trypsin, and chymotrypsin, or Wobe-Mugos preparation of enzymes), and ice chips may be beneficial in preventing or reducing the severity of stomatitis. There is consistent evidence from small high-quality studies that red and infrared low-level laser therapy (LLLT) can partly prevent development of cancer therapy-induced oral mucositis. LLLT also significantly reduced pain, severity,

and duration of symptoms in patients with cancer therapy-induced oral mucositis [99].

Anorexia and Weight Loss

Anorexia may result as much from a loss of appetite caused by cancer as from treatment-related nausea, vomiting, oral pain, diarrhea, and loss or disturbance of taste. Anorexia-related symptoms, which include weakness, fatigue, depression, tooth loss, and organ damage, can have a negative impact on health-related quality of life, can affect a patient's ability to perform daily tasks, and can result in death in severe cases. Pharmacologic intervention may be required in case of severe cachexia; these include megestrol acetate [100], eicosapentaenoic acid diester [101], medroxyprogesterone acetate [102], and mixtures of beta-hydroxyl beta-methyl butyrate, glutamine, and arginine [103].

Gastrointestinal Perforation

Gastrointestinal perforation is a rare but potentially fatal complication that has been reported in association with all the targeted agents except (to date) everolimus [88–91, 93]. The highest rate is seen with bevacizumab as demonstrated in a meta-analysis of 17 randomized studies, including more than 12,000 patients with various cancers, that reported an overall incidence of gastrointestinal perforation of 0.9 % [104]. Risk factors for gastrointestinal perforation include history of past diverticulitis or ulcers, radiation exposure, recent sigmoidoscopy or colonoscopy, gastrointestinal obstruction, and multiple previous surgeries. Gastrointestinal perforation is an indication for immediate discontinuation of anticancer therapy and appropriate treatment of the perforation.

Metabolic Toxicities

Fatigue

Fatigue is a persistent, subjective sense of emotional, physical, and/or cognitive tiredness or exhaustion. Fatigue often results

from multiple causes. It can be a cancer-related side effect, an adverse event of the treatment, as well as the symptom of other conditions, including hypothyroidism, anemia, depression, sleep disturbances, or pain, that are often seen with targeted therapies [105]. Therefore, any underlying cause of fatigue should first be ruled out before making specific recommendation to the patient. Patients should be encouraged to conserve energy, to reschedule activities to periods of peak energy, and to stay active in order to promote sleep. Alternative approaches such as stress management, relaxation techniques, and nutritional support may be useful [106].

Hypothyroidism

Hypothyroidism is a very common side effect of sunitinib [89]. Preexisting hypothyroidism should be detected and treated before starting sunitinib treatment, as recommended in the EU SmPC [89]. There is no consensus on the frequency of thyroid function monitoring under treatment, although initially monthly TSH dosage are advisable [107]. There is no clear recommendation whether these recommendations for thyroid function monitoring should be extended to all patients treated with TKIs.

Hyperglycemia

Hyperglycemia is a very common side effect of the mTOR inhibitors temsirolimus and everolimus [92, 93]. It is recommended to monitor fasting serum glucose before initiating treatment with everolimus or temsirolimus and periodically thereafter. Hyperglycemia should be treated with dietary modifications and an increase in the dose or initiation of insulin and/or hypoglycemic agent therapy.

Cardiovascular Side Effects

Hypertension

Arterial hypertension is a common side effect of inhibitors of the VEGF pathway, reported at a frequency of between 12

and 41 % in patients treated with sorafenib, sunitinib, bevacizumab + IFN-α (alpha), or pazopanib [88–91]. Management of angiogenesis inhibitor-related hypertension should follow the recommendations of the European Society of Hypertension.

Blood pressure (BP) monitoring is mandatory before and during therapy; however, there is general disagreement about when and how BP should be measured [94, 108, 109]. The routine use of home BP monitoring may be valuable in standard care for early detection and accurate assessment of BP changes [108, 109]. Home monitoring can be recommended, but then patients need to be provided with individualized thresholds for contacting their physician. When diagnosed, hypertension should be treated with standard antihypertensive therapy with a preference for angiotensin-converting enzyme (ACE) and inhibitors and angiotensin II receptor blockers (ARBs).

Cardiovascular Events

Initiation of TKIs and inhibitor of the VEGF pathway requires careful monitoring of cardiac effects. Generally, VEGF-targeted agents should be used with caution in any patients with clinically significant cardiovascular disease or preexisting congestive heart failure, and these patients should be closely monitored for clinical signs of heart failure. Periodic measurements of LVEF using echocardiography or magnetic resonance imaging are the recommended methods for monitoring cardiac function during cancer treatment [110–112]. Since cardiac dysfunction can be hampered by other side effects such as hypothyroidism or hypertension, these conditions should be carefully monitored and managed. Except for few anecdotal cases, if is not known whether left ventricular dysfunction is reversible upon treatment cessation.

Venous and Arterial Thromboembolism

Venous thromboembolism (VTE) is a common complication in cancer patients [113, 114]. Risk factors include age older than 65 years, previous VTE events, and surgery. It is not clear whether targeted agents increased the risk of VTE. Although the EU

SmPC for bevacizumab does not mention VTE as a side effect, a meta-analysis of 15 studies investigating the treatment of various solid tumors with bevacizumab suggested an increased incidence of VTE, 12 % for all grades and 6 % for high grade [115]. General recommendations on the prophylaxis and treatment of thrombosis in cancer patients have been produced by ASCO and the American College of Chest Physician [116]. Anticoagulation prophylaxis is not recommended for ambulatory patients with cancer receiving systemic treatment, whether the increased risk of thrombotic events with some targeted agents warrants prophylaxis in ambulatory patients remains unclear. Especially, acetylsalicylic acid or other antiplatelet drugs should be used with caution in association with anti-VEGF agents because of the increased risk of bleeding.

Wound Healing and Hemorrhage

Wound healing is one the most important challenge that surgeons face when confronted with RCC patients treated with targeted therapies. This has been well documented with bevacizumab so that the EU SmPC includes a black box warning recommending treatment discontinuation for at least 28 days in case of surgery. In case of elective surgery, treatment should be discontinued at least 3 weeks before [91]. Signs of wound dehiscence or infection should be regularly monitored. TKIs and mTOR inhibitors may also impair wound healing, although clear data and recommendations on the minimal duration of treatment interruption before or after surgery are still lacking, with suggestions ranging from 7 to 14 days. Of note, one study with TKIs found that in RCC patients undergoing cytoreductive nephrectomy or resection of retroperitoneal recurrence, rates of incision-related complications were similar between patients treated with preoperative sorafenib, sunitinib, or bevacizumab and those who underwent up-front surgery [117].

Minor hemorrhagic events such as epistaxis are common in patients treated with bevacizumab, sunitinib, temsirolimus, and everolimus [89–92]. The impact of minor bleeding events can be limited by good patient education. In contrast, severe life-threatening events are more exceptional, mostly occurring with

bevacizumab. However, it has raised the concern of treating patients' metastases of the central nervous system (CNS) with bevacizumab + IFN-α (alpha). These patients were excluded from the registration trial. TKIs sorafenib and sunitinib can be safely administered to patients with CNS metastases that have been irradiated. One of the primary measures against bleeding is an optimal control of blood pressure to avoid hypertension.

Summary

The unique sensitivity of prostate cancer to hormone therapy and of kidney cancer to therapies targeting the VHL/HIF pathways is creating a unique therapeutic portfolio, which does not include chemotherapy. These classes of drugs share the particularities of having to be prescribed for extended periods of time because they do not eradicate the disease but rather switch it to a more chronic state. Emerging therapies generate the hope of multiple sequential treatments that will effectively prolong the duration of life. Most of their side effects are more bothersome than really morbid, but because these drugs are administered chronically, it may result in profound alteration of the patients' quality of life. Ultimately, this is a threat to compliance and a danger hampering the chronic efficacy of these treatments. In addition, the side effects of many of these drugs often overlap with common, widespread chronic illnesses such as diabetes, hypertension, hypercholesterolemia, and heart failure. Therefore, the management of these side effects is of utmost complexity so that only a multidisciplinary preventive approach involving physicians, nurses, and properly educated patients will guarantee an optimal efficacy.

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