Chapter 5
Impact of Comorbidity on Treatment Decision Making and Outcomes

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Abstract Cancer, like many chronic conditions, is a disease of aging, and more than half of cancer patients in developed countries are 65 years or older. Therefore, many cancer patients have comorbidities, high use of medications, altered body composition, pharmacokinetics, and pharmacodynamics. Therefore, the treatment plans need to be individually tailored to achieve optimal outcomes. This chapter on comorbidity in cancer decision making gives some general principles and then will review some specific comorbidities with their incidence, considerations for decision making and treatment outcome. Scores to assess the risk of toxicity from chemotherapy will also be reviewed. Comorbidity burden is a major influencer of life expectancy and should be integrated in life expectancy estimates. The most assessed comorbidities are renal insufficiency and hepatic diseases. Creatinine clearance should be systematically calculated, and for several types of treatment, the Child-Pugh classification can be used. We also review the treatment of patients with cardiovascular diseases, auto-immune/inflammatory diseases, and diabetes. All risk factors of comorbidity should be comprehensively evaluated before cancer treatment, in order to reduce treatment-related toxicity and improve patient outcomes. Future research should address how to integrate the impact of multiple concomitant comorbidities, and more specifically which subgroups most affect various cancer outcomes.

Keywords Comorbidity · Elderly · Cancer · Clinical decision making · CRASH score · Life expectancy · Renal function · Hepatic function · Geriatric oncology

Key Points

- Many cancer patients have concomitant comorbidity. More than 90 % of cancer patients aged 70 and above have at least one comorbidity
- Comorbidity is a major influencer of life expectancy, and an individualized estimation of life expectancy should be conducted

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- Comorbidity influences the behavior and outcomes of cancer and its treatment
- Creatinine clearance should always be calculated, as older patients can have serious limitations of renal function with normal creatinine levels
- Many of the new targeted therapies have a cardiovascular impact and should be used with caution in patients with cardiovascular disorders
- In diabetic patients receiving short-duration steroids, as given in many chemotherapy regimens, a combination of insulin detemir and aspart leads to better glycemic control than sliding scale insulin
- Risk indexes, such as the Chemotherapy Risk Assessment Score for High-age patients (CRASH) score and the Cancer and Aging Research Group (CARG score), exist to help assess the individual patient risk of toxicity from chemotherapy
- More research work in patients with multimorbidity needs to be done to assess which subgroup most influences outcome.

5.1 Introduction

Cancer, like many chronic conditions, is a disease associated with aging, and more than half of the cancer patients in the USA are 65 years or older [1]. Therefore many cancer patients have comorbidities [2–4], a high use of medications [5, 6], altered body composition, pharmacokinetics, and pharmacodynamics [7–9]. In such patients the treatment plans need to be individually tailored.

Many clinical trials have reported benefits for the inclusion of older cancer patients compared to younger patients with adequate cancer treatment in many solid tumors and hematologic malignancies, sometimes at the cost of some increased toxicity. However, these selected older patients typically have a low level of comorbidity. How then, can we transfer the evidence to patients with comorbidities? Is there direct evidence generated in patients with comorbidities? This chapter on comorbidity in cancer decision making will address two aspects: how the comorbidity burden of a patient affects life expectancy and fitness; and highlights of specific comorbidities with their incidence, considerations for decision making and treatment outcomes. Moreover, the MAX2 index and CRASH score for predicting chemotherapy-induced toxicity will be introduced.

5.2 General Considerations

The comorbidity burden of cancer patients can considerably influence their life expectancy. Walter et al. [10] demonstrated large variations in life expectancy between the top and the bottom quartile of the US population for similarly aged

patients. A more detailed analysis of the impact of comorbidity using the Charlson Comorbidity Index in the SEER/Medicare registry is also available [11]. Validated geriatric tools are available online to help us estimate a patient's 1-year, 5-year, or 10-year risk of death if they are aged 65 or more. www.ePrognosis.org. This can be particularly helpful when deciding what adjuvant treatment to choose for patients in their late seventies or eighties. When deciding adjuvant treatment, it is also very important to know the time dynamic of the risk of relapse. For example, the risk of relapse of an estrogen-receptor positive breast cancer is fairly constant over a long period of time, whereas the risk of relapse from colon cancer is mostly in the first 5 years [12]. Although more research still needs to be done to quantify this effect, comorbidity does contribute to a decrease of functional reserve that is linked to frailty. Several frailty indexes integrating comorbidity have been studied in cancer patients [13–15].

As comorbidity is a multidimensional construct, quantifying it in order to assess its impact is a challenge. Most validated indices have used either mortality risk as an endpoint (e.g. Charlson Comorbidity Index [16], Kaplan-Feinstein Index [17]), or an expert assessment of the functional and mortality impact of the diseases (Cumulative Illness Rating Scale-Geriatric (CIRS-G) [18, 19], Index of Coexistent Diseases (ICED) [20]). Every comorbidity has a more detailed specific severity rating, but in this review we chose to address to overall comparison ratings in the context of oncology.

Another issue related to comorbidity is polypharmacy. Older American cancer patients take an average of six medications, two of them interacting with the CYP450 cytochrome system [21]. As an increasing number of chemotherapies and targeted agents are liver metabolized, careful attention should be paid to a review of the patient's medications and to eliminating superfluous prescriptions, or replacing some medications with others less likely to interact with the intended cancer treatment drug. The presence of high level drug interactions significantly increases the risk of severe toxicity from chemotherapy [22].

5.3 Individual Comorbidities

5.3.1 Renal Function

5.3.1.1 Renal Insufficiency and Its Incidence

According to Cumulative Illness Rating Scale-Geriatrics (CIRS-G) [18], kidney as comorbidity is considered as one category (Table 5.1). There are five rating scores which range from 0—no problem to 4—with dialysis. Their severity is determined by serum creatinine levels and depends on the treatment. In the Kaplan-Feinstein Index (KFI) [17], renal dysfunction is considered as a cogent comorbidity and its severity is defined to have proteinuria, azotemia, and renal decompensation. Adult

Table 5.1 Assessment of renal insufficiency in several comorbidity indexes

Measurement	Grade 1	Grade 2	Grade 3	Grade 4
CIRS-G	History of kidney stone passage within 10 years or asymptomatic kidney stone; pyelonephritis within five years	Serum creatinine >1.5 but <3.0 without diuretic or antihypertensive medication	Serum creatinine >3.0 or serum creatinine >1.5 in conjunction with diuretic, antihypertensive, or bicarbonate therapy' current pyelonephritis	Requires dialysis; renal carcinoma
Kaplan-Feinstein index	Proteinuria (tests of 3+ or 4+ on two or more urinalyses, or excretion of 1 g on 24-h urine collection); recurrent lower urinary infections or renal stones	Azotemia, manifested by elevated BUN (>25 mg%) and/or creatinine (>3.0 mg%) without secondary effects; nephrotic syndrome; recurrent infections; hydronephrosis	Uremia, renal decompensation with secondary anemia, edema, hypertension	–
AEC-27	Creatinine 2–3 mg/dl; stable transplant >6 months ago	Creatinine >3 mg/dl; stable transplant ≤6 months; chronic dialysis	Creatinine >3 mg/dl with multiple organ failure, shock, or sepsis; acute transplant rejection, acute dialysis	–
NCI/NIA Life-Threat Model	–	–	–	Renal failure
Charlson comorbidity index	–	Moderate or severe renal disease; serum creatinine >3 mg/dL; dialysis; transplantation; uremic syndrome	–	–

Comorbidity Evaluation-27 (ACE-27) [23] includes renal disease as comorbidity with four levels of severity of none to severe and the Index of Coexistent Disease (ICED) scales [20] with four levels of severity.

In the National Cancer Institute/National Institute on Aging (NCI/NIA) Life-Threat Model [24], renal failure is considered a high impact comorbidity, even without active management. In the Charlson comorbidity index (CCI) [25], renal disease including elevated creatinine, dialysis, and transplantation rates '2 points' (Table 5.1).

Among cancer patients, the incidence of renal insufficiency remains unclear. High prevalence of renal insufficiency in cancer patients has been observed by French investigators of the Renal Insufficiency and Cancer Medicine (IRMA) Study Group [26]. It was somewhat different depending on the methods used to calculate the renal function. The prevalence was 57.5 % using Cockcroft-Gault or 52.9 % with the abbreviated Modification of Diet in Renal Disease (aMDRD). Renal insufficiency was defined to be less than 90 mL/min of GFR by the Working Group of the National Kidney Foundation [27]. Stage 3 (GFR of 30–59 mL/min) or higher (GFR of less than 30 mL/min) renal insufficiency made up about 20 % by both of methods. According to the IRMA study group, a high prevalence of renal insufficiency of 60.3 % was observed in cancer patients who had normal serum creatinine, when this was calculated according to the Cockcroft-Gault formula. Furthermore, the prevalence of renal insufficiency in cancer patients aged 75 years and older was 74.1 %, as calculated by the MDRD formula.

5.3.1.2 Treatment Decision Making with Renal Insufficiency

Estimating Renal Function

Renal function should be assessed by calculation of GFR or creatinine clearance (CrCl) in all patients, even if serum creatinine levels are within normal range [28]. For assessment of renal function, we should consider sex, age, and weight of the patient for parameters of representing the muscle mass of the patient. There are various formulae to estimate GFR or CrCl. The SIOG renal insufficiency task force recommends the abbreviated MDRD (aMDRD) formula or the Cockcroft-Gault formula for older cancer patients [29].

Dose Adjustment Recommendation

Kintzel and Dorr [30] provided recommendation for 17 drugs which had a renal clearance equal to or exceeding 30 % of the administered dose out of 48 anticancer drugs reviewed. Recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency were developed by the International Society of Geriatric Oncology (SIOG) taskforce on the basis of the Kintzel and Dorr study [31]. In those studies, the alkylating agents included carmustine, ifosfamide, melphalan, dacarbazine, and temozolomide. The platinum agents were carboplatin, cisplatin, and oxaliplatin. The antimetabolites fludarabine, methotrexate, capecitabine, cytarabine, hydroxyurea, raltitrexed, and pemetrexed were also reviewed. As

topoisomerase inhibitors, etoposide and topotecan were included. Beside anticancer drugs, they suggested guidelines for bisphosphonates, including zoledronic acid, pamidronate, and ibandronate.

Furthermore, the guidelines for anticancer drugs with limited renal excretion were suggested. They were chlorambucil in alkylating agents, gemcitabine and fluorouracil in antimetabolites, vincristine, vinblastine, and vinorelbine in vinca alkaloids, paclitaxel, ABI 007, and docetaxel in taxanes, irinotecan in topoisomerase inhibitors, doxorubicin, liposomal doxorubicine, epirubicin, daunorubicine, mitoxantrone, mitomycin, and idarubicin in antitumor antibiotics, tamoxifen and-bicalutamide in hormonal therapy, and thalidomide, bortezomib, and anti-VEGF antibiodies in other drugs.

Other Considerations for Patients with Renal Insufficiency

Beside estimating renal function, an assessment and optimization of hydration status should be performed per SIOG recommendation for renal insufficiency in older cancer patients, as renal insufficiency affects the ability of the body to control the fluid balance [32]. They also recommended that co-administration of known nephrotoxic drugs such as NSAIDs or Cox-2 inhibitors should be avoided or minimized.

5.3.1.3 Life Expectancy and Outcomes

In a study of the effects of unidentified renal insufficiency in metastatic colorectal cancer patients treated with capecitabine in combination with oxaliplatin, all the patients had normal values of serum creatinine and the ranges of GFR were very broad, from <30 to >90 mL/min [33]. The patients with GFR of 60 mL/min or less experienced more severe toxicities with cytopenia (76 % vs. 61 %, OR = 1.86, $p < 0.001$), diarrhea (34 % vs. 29 %, OR = 3.76, $p = 0.007$), stomatitis (10 % vs. 6 %, OR = 2.81, $p = 0.002$), and hand-foot syndrome (18 % vs. 11 %, OR = 2.56, $p = 0.045$) than those with GFR of 60 mL/min or more. The response rate and time to progression (4.5 vs. 5.5 months, HR = 1.57, $p = 0.015$) were significantly lower in renal insufficiency patients. Unidentified renal insufficiency patients received more dose modification (34 % vs. 14 %, OR = 1.98, $p < 0.001$) and dose interruption (52 % vs. 26 %, OR = 1.72, $p < 0.001$). The authors of this study suggested that estimating renal function with GFR should be required for all metastatic colorectal cancer patients before initial chemotherapy.

A retrospective Japanese study of advanced urothelial cancer, reported that 3-year overall survival for patients having GFR ≥60 mL/min/1.73 m^2 was better than that for those with GFR of <60 mL/min/1.73 m^2, when treated with a gemcitabine and cisplatin combination therapy (31.4 % vs. 14.1 %) [34]. The reason was a high dose reduction rate of gemcitabine and cisplatin (43.9 %). The 1-year survival of patients with a reduced dose of the two drugs was significantly lower

than that for those treated with standard-dose among the patients with an estimated GFR of <60 mL/min/1.73 m^2 (26.2 % vs 60.3 %, $p = 0.01$).

An advanced non-small cell lung cancer study by Langer et al. demonstrated that patients with mild (GFR of 51–80 mL/min) or moderate (GFR of 50 mL/min or less) renal insufficiency had response rates and toxicity similar to patients with normal renal function, when treated with weekly nab-paclitaxel (100 mg/m^2) or paclitaxel 200 mg/m2 every three weeks, in combination with carboplatin (AUC = 6 every three weeks) [35]. The median dose intensity and cumulative exposure was better for nab-paclitaxel weekly across all levels of renal function. Other outcomes were comparable as well.

An ancillary study of CALGB 49907, which randomized older breast cancer patients to capecitabine vs. AC or CMF analyzed the impact of renal function on outcomes [36]. Patients with an estimated creatinine clearance (Cockroft-Gault) ≥30 ml/min were enrolled. Methotrexate and capecitabine were dose-adapted to renal function. With this dose-adaptation, renal function did not predict whether a patient would receive a dose modification, complete treatment per protocol, or experience hematologic toxicity for any regimen. It was however associated with non-hematologic toxicity in a heterogeneous fashion: increased creatinine clearance was associated with a decreased risk of toxicity in patients receiving AC, and an increased risk of toxicity in patients receiving capecitabine. It was not predictive of RFS or OS.

5.3.2 Hepatic Function

5.3.2.1 Hepatic Dysfunction and Its Incidence

According to Cumulative Illness Rating Scale-Geriatrics, liver diseases as comorbidity are considered as one category (Table 5.2). There are five rating scores which range from 0 with no problem to 4 with active hepatitis. Their severity is determined by a liver function test, including bilirubin and depending on their activity. The Kaplan-Feinstein Index considers hepatic dysfunction as a cogent comorbidity and its severity is defined by laboratory findings and clinical manifestation. Adult Comorbidity Evaluation-27 includes liver disease as comorbidity with four levels of severity of none to severe. The index of Coexistent Disease scales includes hepatobiliary disease with four levels of severity.

In the National Cancer Institute/National Institute on Aging Life-Threat Model, liver dysfunction is considered as a low to moderate impact comorbidity depending on active management. The Charlson comorbidity index takes liver disease into account, including liver cirrhosis without portal hypertension or with portal hypertension and rates '1 or 3 of points' (Table 5.2).

Unfortunately, most clinical trials have excluded patients with hepatic dysfunction. So, the prevalence of hepatic dysfunction is poorly known in cancer patients. Besides comorbidities, hepatic dysfunction also results from the

Table 5.2 Assessment of hepatic dysfunction in several comorbidity indexes

Measurement	Grade 1	Grade 2	Grade 3	Grade 4
CIRS-G	History of hepatitis >five years ago	Mildly elevated LFT (up to 150 % of normal); hepatitis within five years; daily or heavy alcohol use within five years	Elevated bilirubin (total >2); marked elevation of LFT (>150 % of normal)	Active hepatitis
Kaplan-Feinstein index	Chronic liver disease manifested on biopsy or by persistently elevated BSP (>15 % retention) or bilirubin (>3 mg%)	Compensated hepatic failure (cutaneous spiders, palmar erythema, hepatomegaly or other clinical evidence of chronic liver disease)	Hepatic failure (ascites, icterus, encephalopathy); or esophageal varices	–
AEC-27	Chronic hepatitis or cirrhosis w/o PHT; chronic liver on biopsy or with bilirubin >3 mg/dl	Chronic hepatitis, cirrhosis, PHT with moderate symptoms "compensated hepaticfailure"	PHT and or esophageal bleeding $\underline{<}$6 months (encephalopathy, ascites, jaundice with bilirubin >2; h/o transplant ≤6 months or acute rejection	–
NCI/NIA Life-Threat Model		No current management/history only	Under active management	–
Charlson comorbidity index	Mild liver disease; cirrhosis without PHT; chronic hepatitis	–	Moderate or severe liver disease; cirrhosis with PHT± variceal bleeding	–

LFT liver function test; *PHT* portal hypertension

metastases of solid tumors, including breast cancer, lung cancer, and colorectal cancer to the liver. A retrospective study of the association of comorbidity with survival and treatment-related toxicities reported that the incidence of liver disease as comorbidity was 30.8 %, which included biliary disease and pancreatic disease as assessed by CIRS-G [37]. Grade 3 or 4 of hepatic dysfunction made up 7.3 % in this study. According to annual report by the NIH, incidence of hepatic dysfunction, including liver cirrhosis, chronic hepatitis, and moderate to severe liver disease, was

0.8 % in breast cancer, colorectal cancer, lung cancer, and prostate cancer patients of 65 years and older [38]. A retrospective study of nonhepatic cancer in patients with liver cirrhosis reported 19.8 % of the incidence of nonhepatic cancer [39].

5.3.2.2 Treatment Decision Making with Hepatic Dysfunction

Similar to estimating renal function with creatinine or creatinine clearance, hepatic dysfunction has been estimated with laboratory findings including the level of bilirubin, albumin, and prothrombin time and clinical manifestation including ascites, encephalopathy, nutritional status, peripheral edema, and complications of portal hypertension. Hepatic dysfunction affects the hepatic clearance of drugs, low albumin increases the fraction of free drug, and portal hypertension affects drug absorption.

Estimating Hepatic Dysfunction

There are several classifications for estimating hepatic function, but no single test has been developed for clinical use to adjust drugs in patients with hepatic dysfunction. The Child-Pugh classification (Table 5.3) is one of the best known assessments for hepatic dysfunction. Assessment of the Child-Pugh classification results in (A) mild degree with 5 or 6 points, (B) moderate degree with 7–9 points, or (C) severe degree with 10–15 points.

The model for end-stage liver disease (MELD) is based on serum bilirubin, serum creatinine, the internationalized ratio (INR) of prothrombin time, and the underlying liver disease. The MELD score accurately predicts 3-month mortality for patients on a liver transplant waiting list.

The Maddrey discriminant function (df) is for patients with acute alcoholic hepatitis, the disease is not severe if df < 54, is severe when the score is between 55

Table 5.3 Child-Pugh classification

Variables	1 point	2 points	3 points
Encephalopathy grade[a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, mg/dL	<2	2–3	>3
Serum albumin, g/L	>3.5	2.8–3.5	<2.8
Prothrombin time, s prolonged	<4	4–6	>6

[a]Grade 0: Normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per second) waves
Grade 2: Lethargic, time-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: Unrousable coma, no personality/behavior, decerebrate, slow 2–3 cps delta activity

and 92, and probably lethal when 93 or more and left untreated. The df is calculated as follows:

$$\mathrm{df} = 4.6 \times (\text{prothrombin time, in seconds}) + \text{serum total bilirubin, mg/dL}$$

As another markers of hepatic function, Indocyanine Green clearance correlated significantly with Child-Pugh's classification (r = 0.86, $p = 0.0001$) and antipyrine clearance correlated significantly with Child-Pugh's classification (r = 0.67, $p = 0.0003$).

Dose Adjustment Recommendation

There are three classifications for the hepatic contribution to the elimination of the drug which are: no hepatic contribution, limited (<20 %) hepatic elimination, and extensive (>20 %) hepatic elimination.

Taxanes, vinca alkaloids, irinotecan, and anthracyclines may generate unacceptable toxicity in patients with poor hepatic function. Continuous infusion of 5-fluorouracil, capecitabine, mechlorethamine, cyclophosphamide, topotecan, and oxaliplatin are relatively well tolerated in patients with hepatic dysfunction [40].

Both the Food and Drug Administration (FDA) and the European medicines Agency (EMEA) have published an industry guideline about pharmacokinetics of medical products in patients with impaired hepatic function. These guidelines recommend that the Child-Pugh classification could categorize patients according to their degree of hepatic dysfunction and exogenous markers might be used to assess the elimination capacity by different mechanisms.

Some general considerations were recommended by Verbeeck for patients with hepatic dysfunction [41] and can apply to anticancer agents as well:

1. Drugs with a relatively high hepatic extraction ratio: the oral bioavailability of these drugs can be drastically increased in patients with chronic liver disease, and the dosage should be reduced accordingly. Following systemic administration (iv, im, sc, etc.), the plasma clearance may be reduced if hepatic blood flow is decreased.
2. Drugs with a low hepatic extraction and high plasma protein binding (>90 %): the oral and intravenous clearance of these drugs is determined by the intrinsic capacity of the hepatic elimination mechanisms and the unbound drug fraction in blood or plasma. The intrinsic clearance will be reduced to a degree determined by the fractional status of the liver and the specific metabolic pathways involved in the elimination of the drug. Because the unbound fraction of drug in blood or plasma may be significantly increased in patients with chronic liver disease, pharmacokinetic evaluation should be based on the unbound blood/plasma concentrations and dosage adjustment may be necessary even though total blood/plasma concentrations are within the normal range.

3. Drugs with a low hepatic extraction ratio and low plasma protein binding (<90 %): the oral and intravenous clearance of these drugs is determined by the intrinsic capacity of the hepatic elimination mechanisms and unbound drug fraction in blood or plasma. The intrinsic clearance will be reduced to a degree determined by the functional status of the liver and the specific metabolic pathways involved in the elimination of the drug. Fluctuations in the unbound drug fraction in blood or plasma are rather small and will not significantly affect blood/plasma clearance of the drug. Dosage adjustment may be necessary and should be aimed at maintaining normal total (bound and unbound) plasma concentrations.
4. The elimination of drugs that are partly excreted in unchanged form by the kidneys will be impaired in patients with the hepato-renal syndrome. It should be taken into account that creatinine clearance significantly overestimates glomerular filtration rate in these patients.
5. The volume of distribution of hydrophilic drugs may be increased in patients with chronic liver disease who have edema or ascites. As a consequence, the loading dose may have to be increased in these patients if a rapid and complete effect of the drug is required. Since many hydrophilic drugs are eliminated primarily in unchanged form by the kidneys, renal function should be taken into consideration.
6. Extreme caution is recommended when using drugs with a narrow therapeutic index in patients with liver disease and when administering any drug to patients with severe liver dysfunction (Child-Pugh class C).

5.3.2.3 Life Expectancy and Outcomes

In a prospective study of the impact of liver cirrhosis on the outcome of ovarian cancer, compensated liver cirrhosis (Child-Pugh class A) affected neither disease-free survival (95 % CI, 19.9–26.7 months vs. 19.4–26.1 months, $p = 0.719$) nor overall survival (95 % CI, 21.6–25.7 months vs. 21.1–25.1 months $p = 0.524$) in ovarian cancer patients treated with debulking surgery followed by adjuvant chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC, 5) compared those without liver disease [42].

An Italian study of established cirrhosis and hepatocellular carcinoma treated with sorafenib demonstrated that treatment duration or incidence of adverse event between Child-Pugh class A and class B were not significantly different [43]. A retrospective study of sorafenib for advanced hepatocellular carcinoma patients with Child-Pugh class B liver cirrhosis observed that overall survival was significantly different among class A, class B score 7, and class B score 8–9 (6.1 vs. 5.4 vs. 2.7 months, $p = 0.002$) but progression-free survival was similar among them (3.2 vs. 3.2 vs. 2.3 months, $p = 0.26$) [44]. Among them, most of adverse events

had a similar incidence except anemia, gastrointestinal bleeding and hepatic encephalopathy, which developed in class B score 8–9.

A retrospective study investigated prevalence, complication after oncologic treatment, and prognostic predictors of nonhepatic cancer in patients with liver cirrhosis [39]. The prevalence of nonhepatic cancer was 19.8 % and was mainly colorectal cancer, prostate cancer, and tobacco-related cancers. Low bilirubin ($p = 0.01$), normal albumin ($p = 0.005$), and absence of ascites ($p < 0.0001$) were related significantly to longer survival. In that study, Child-Pugh classification and MELD score were suitable parameters to predict mortality. The rate of post-interventional death after specific treatment was high although all patients with long-term survival received specific oncologic treatment.

5.3.3 Immunologic Disorders

5.3.3.1 Immunologic Disorders and Their Incidence

Examples of autoimmune diseases are rheumatic arthritis, systemic lupus erythematosus, antiphospholipid syndrome, multiple sclerosis, scleroderma, primary biliary cirrhosis, autoimmune hepatitis, Graves' disease, Hashimoto's thyroiditis, and Sjogren's disease. Immunologic disorders usually involve joint organs and most of the assessments of comorbidity classify immunologic diseases in the musculoskeletal category.

According to Cumulative Illness Rating Scale-Geriatrics, autoimmune disease is considered to be in the musculoskeletal/integument category (Table 5.4). There are five rating scores which range from 0 with no problem to 4 with severe joint deformity. Their severity is determined by their function of activity in daily life. In the Kaplan-Feinstein Index, locomotive impairment is considered as a cogent comorbidity and its severity is defined by the level of limitation of activity. The Adult Comorbidity Evaluation-27 includes rheumatologic disease as comorbidity with four levels of severity of none to severe. The Index of Coexistent Disease scale includes arthritis with four levels of severity.

In the National Cancer Institute/National Institute on Aging Life-Threat Model, arthritis is considered as a negligible to low impact comorbidity, depending on active management. In the Charlson comorbidity index, connective tissue disease, including systemic lupus erythematosus (SLE), polymyositis, mixed connective tissue disease (CTD), polymyalgia rheumatica, and moderate to severe rheumatoid arthritis (RA) rate 1 point.

In this chapter, we will focus on rheumatoid arthritis as an example of autoimmune diseases (Table 5.4).

According to a cancer registry study by Piccirillo et al. [23], the prevalence of reported rheumatologic disease was 1.8 % in cancer patients. By annual report including four solid tumors patients of 65 years and older diagnosed between 1992 and 2005, the incidence of rheumatologic disease was 2.0 % [38]. A study of

Table 5.4 Assessment of immunologic disorder in several comorbidity indexes

Measurement	Grade 1	Grade 2	Grade 3	Grade 4
CIRS-G	Uses prn meds for arthritis; mild limited ADL's from joint pathology	Daily antiarthritic meds; use of assistive devices; moderate limitation in ADL's	Severely impaired ADL's secondary to arthritis; requires steroids for arthritic condition	Wheelchair bound' severe joint deformity or severe impaired usage
Kaplan-Feinstein Index	Slightly impaired (some limitation of activity)	Moderate impaired (confined to home, nursing home, or convalescent setting)	Bed-to-chair existence	–
AEC-27	CTD on NSAIDS or no treatment	CTD on steroids or immunosuppressant medications	CTD with secondary end-organ failure (renal, cardiac, CNS)	–
NCI/NIA Life-Threat Model	No current management/history only: arthritis	Under active management: arthritis	–	–
Charlson comorbidity index	SLE; polymyositis; mixed CTD; polymyalgia rheumatic; moderate to severe RA	–	–	–

ADL activity of daily livings; *CTD* connective tissue disorder

Hodgkin's lymphoma with pre-existing autoimmune disease reported an incidence of autoimmune diseases to be 2.7 % among [45]. On the other hand, cancer incidence among patients with rheumatoid arthritis has been reported as high, especially lymphoid malignancies (standardized incidence ratios, SIR = 2.0, 95 % CI, 1.5–2.6) [46].

5.3.3.2 Treatment Decision Making with Immunologic Disorders

Cancer patients may develop rheumatic manifestations after chemotherapy [47]. Patients receiving adjuvant chemotherapy with cyclophosphamide combined with either methotrexate and fluorouracil or doxorubicin and fluorouracil experienced myalgia, arthralgia, and tenosynovitis [48]. Tamoxifen has been known to be associated with occasional rheumatic symptoms [49]. Aromatase inhibitors can be associated with arthralgias and tenosynovitis [50] Bleomycin, vinblastine, cisplatin,

5-fluorouracil have been associated with Raynaud's phenomenon [51, 52]. Interferon-α and -γ have been associated with the generation of auto-antibodies and the induction of autoimmune disorders [53–55]. Recently developed checkpoint inhibitors, for example, ipilimumab, pembrolizumab, nivolumab and lambrolizumab, have toxic immune-mediated effects such as pneumonitis, colitis, and hepatitis [56–58], linked to their mechanism of breaking immune tolerance. Patients with preexisting autoimmune disorders were excluded from clinical trials, and therefore no information is available about the potential of these drugs for flare ups of an underlying autoimmune disease.

5.3.3.3 Life Expectancy and Outcomes

In a prospective study of survival outcomes in non-Hodgkin's lymphoma patients with rheumatoid arthritis, RA patients with NHL had similar overall survival compared with non-RA controls (HR = 0.95, 95 % CI, 0.70–1.30) [59]. In the study, RA with HNL had low risk of lymphoma progression or relapse (HR = 0.41, 95 % CI, 0.25–0.68) and of lymphoma or treatment-related death (HR = 0.60, 95 % CI, 0.37–0.98), but had a more than double the risk of death from causes unrelated to lymphoma, compared with non-RA controls (HR = 2.16, 95 % CI, 1.33–3.50). The median duration of RA disease was 14 years and 95 % of RA patients had prior Disease-Modifying Anti-Rheumatic Drug (DMARD) use, including methotrexate, hydroxychloroquine, gold salt, sulfasalazine, azathioprine, and others.

A study of survival patterns in patients with Hodgkin's lymphoma with a pre-existing autoimmune disease observed that Hodgkin's lymphoma patients with autoimmune disease had a high risk for death compared with those without autoimmune disease (HR = 1.8, 95 % CI, 1.3–2.4 for women, and HR = 1.7, 95 % CI, 1.3–2.2 for men) [45]. The most common causes of death were lymphoma and treatment-related complications (76 % of women and 68 % of men) in the study.

5.3.4 Cardiovascular Disorders

5.3.4.1 Cardiovascular Disorders and Their Incidence

Cardiovascular diseases are coronary artery disease, congestive heart failure, arrhythmia, valvular disease, pericardial disease, hypertension, and peripheral atherosclerotic disease.

According to Cumulative Illness Rating Scale-Geriatrics, heart and vascular comorbidity are separate categories (Table 5.5). There are five rating scores which range from 0—no problem to 4—intractable congestive heart failure for heart category or previous surgery for vascular category. The Kaplan-Feinstein Index considers cardiovascular disorder as a cogent comorbidity and its ailments are

Table 5.5 Assessment of cardiovascular disorders in several comorbidity indexes

Measurement	Grade 1	Grade 2	Grade 3	Grade 4
CIRS-G Heart category	Remote MI (>5 years ago); occasional angina treated with prn meds	CHF compensated with meds; daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation; bundle branch block; daily antiarrhythmic drugs	Previous MI < 5 years; abnormal stress test; s/p PCA or CABG; bifasicular block; pacemaker for cardiogenic syncope	Marked activity restriction secondary to cardiac status (i.e., unstable angina or intractable congestive heart failure)
CIRS-G Vascular category	Hypertension compensated with salt restriction and weight loss; serum cholesterol with normal range	Daily antihypertensive meds; one symptom of atherosclerotic disease (angina, claudication, bruit, amaurosis fugax, absent pedal pulses); aortic aneurysm <4 cm	Two or more symptoms of atherosclerosis; two or more antihypertensive drugs for control; evidence of left ventricular hypertrophy	Previous surgery for vascular problem; aortic aneurysm >4 cm
Kaplan-Feinstein Index Cardiac ailment	MI more than 6 months ago; ECG evidence of coronary disease; or atrial fibrillation	CHF more than 6 months ago; or angina pectoris not requiring hospitalization	Within past 6 months; CHF, MI, significant arrhythmias, or hospitalization required for angina pectoris or angina-like chest pain	–
Kaplan-Feinstein Index Hypertension	DBP 90-114 mmHg, without secondary effects or symptoms	DBP 115-129 mmHg; or at any level below 130, with secondary cardiovascular or symptomatic effects such as headaches, vertigo, epistaxis	Severe or malignant; papilledema; encephalopathy; or DBP 130 mm Hg or higher	–
Kaplan-Feinstein Index Peripheral vascular ailment	Old amputation; intermittent claudication	Recent amputation or gangrene of extremity	–	–
AEC-27 MI	Old MI on ECG only, age undetermined	MI >6 months ago	MI ≤6 months	–

(continued)

Table 5.5 (continued)

Measurement	Grade 1	Grade 2	Grade 3	Grade 4
CAD	ECG/stress/angio evidence of CAD without symptoms; angina not requiring hosp.; CABG, PCA, stent >6 months prior	Chronic exertional angina; CABG, PCA, stent ≤6 months	Unstable angina	
CHF	CHF with dyspnea that responded to TX; exertional dyspnea, paroxysmal mocturnal dyspnea	Hosp for CHF >6 months prior; CHF w/dyspnea limiting ADLs	Hosp for CHF < 6 months; EF <20 %	
Arrhythmias	Sick sinus syndrome	Ventricular arrhythmia >6 months ago; chronic AFib/flutter; pacemaker	Ventricular arrhythmia ≤ 6 months ago	
Hypertension	DBP 90–114; DBP <90 on medication	DBP 115–129; Secondary CV symptoms: vertico, epistaxis, HA	DBP >130; severe malignant papilledema/eye changes; encephalopathy	
Venous disease	Old DVT no longer treated	DVT controlled with Coumadin or heparin; old PE >6 months	Recent PE ≤6 months; venous filter for PE	
PAD	Intermittent claudication; untreated thoracic or abdominal aneuvrysm (<6 cm); s/p abdominal or thoracic aortic repair	Bypass or amputation for gangrene or arterial insufficiency >6 months ago; chronic insufficiency	Bypass or amputation for gangrene or arterial insufficiency ≤ 6 months ago; untreated thoracic or abdominal aneurysm >6 cm	

(continued)

Table 5.5 (continued)

Measurement	Grade 1	Grade 2	Grade 3	Grade 4
NCI/NIA Life-Threat Model		No current management/history only; arrhythmias, hypertension	No current management/history only; angina, MI, valvular disease: Under active management; DVT, hypertension	No current management/history only; cardiac arrest, congestive heart failure Under active management; angina, arrhythmias, cardiac arrest, CHF, MI, valve disease
Charlson comorbidity index	History of MI, symptomatic CHF with response to specific treatment; intermittent claudication, peripheral arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (≥6 cm)	–	–	–

AFib atrial fibrillation, *CABG* coronary artery bypass graft; *CAD* coronary artery disease, *CHF* congestive heart failure; *DBP* diastolic blood pressure; *DVT* deep vein thrombosis; *HA* headaches; *hosp.* hospitalization; *MI* myocardial infarct; *PAD* peripheral arterial disease, *PCA* percutaneous angioplasty

divided into cardiac, hypertension, and peripheral vascular disease. Adult Comorbidity Evaluation-27 includes 7 categories of cardiovascular diseases, which are hypertension, angina, myocardial infarction, arrhythmias, congestive heart failure, peripheral vascular disease, and venous disease as comorbidity with four levels of severity from none to severe. The Index of Coexistent Disease scales includes five categories of cardiovascular diseases, which are organic heart disease, ischemic heart disease, primary arrhythmias and conduction problems, congestive heart failure, and hypertension with four levels of severity.

In the National Cancer Institute/National Institute on Aging Life-Threat Model, cardiovascular disorder is considered as low to high impact comorbidity, depending on disease severity and active management. By the Charlson comorbidity index, cardiovascular disease, including myocardial infarct, congestive heart failure, and peripheral vascular disease, rates 1 point.

The prevalence of cardiovascular disease has been reported ranging from 12 % to 60 % in cancer patients [60]. According to a cancer registry study by Piccirillo et al., the prevalence of hypertension was 40.2 %, and the most common comorbidity in cancer patients [23] and a 71.9 % prevalence of cardiovascular disorders was observed. By annual report, including four solid tumors patients with 65 years and older diagnosed between 1992 and 2005, the incidence of cardiovascular disease was 17.3 %, including 9.7 % of congestive heart failure, 4.3 % of peripheral vascular disease, and 3.3 % of myocardial infarction [38]. The prevalence of the CIRS-G heart category in a secondary analysis of clinical trials including six solid tumors, was 36.3 % and that of the vascular category was 78.4 % [37].

5.3.4.2 Treatment Decision Making in Patients with Cardiovascular Disorder

Numerous chemotherapies, targeted therapies, and hormonal therapies are associated with cardiovascular toxicity, and have been reviewed by others [61–64]. The literature is sparser concerning the management of patients with pre-existing cardiovascular disease.

Congestive Heart Failure (CHF)

CHF is mostly an issue with anthracycline-based regimens. Older patients are at higher cumulative risk of CHF with anthracyclines. A study by [65] showed that while the risk of CHF was low up to 400 mg/m^2 for all patients, patients aged over 65 had a HR of 3.28 of developing CHF beyond that cumulative threshold, compared to younger patients. Whereas for some diseases, such as breast cancer, some good alternatives exist, for other diseases, such as diffuse large B-cell lymphoma (DLBCL), no first line regimen has demonstrated the same curative potential as CHOP-R. In a recent review of 859 DLBCL patients, about 5 % had a preexisting heart failure, half systolic, half diastolic. Patients with diastolic heart failure

received CHOP-like regimens more frequently than the others. 24 % of cardiac events were observed, defined as hospitalization for CHF, for cerebrovascular insult, for chest pain, for ischemic or non-ischemic cardiac events or cardiac-related deaths, in the group treated with R-CHOP, vs. 16.7 % in the non-R-CHOP group, but this was not statistically significant (p value 0.7), given low patient numbers. Overall, 90.9 % of the patients treated with a non-R-CHOP chemotherapy completed the planned treatment versus 58.3 % in the R-CHOP group (p value 0.09). Although patients treated with a R-CHOP regimen tended to have higher complete remission rates compared to non R-CHOP regimens (73.7 % vs. 55.5 % respectively), this result was not statistically significant ($p = 0.37$), and there was no significant difference in overall survival or 2-year relapse free survival, but the numbers were small [66]. Regimens needing intense hydration can be a challenge, especially in patients with decreased diastolic relaxation.

To minimize the anthracycline cardiotoxicity, one can use less cardiotoxic therapies, for example continuous infusion, use of epirubicin, desrazoxane, liposomal anthracycline formulation, or sequential administration of conventional anthracyclines and trastuzumab in HER2-positive breast cancer [67].

Coronary Artery Disease

A large SEER registry study identified coronary artery disease as a risk factor for chemotherapy-induced CHF in older women (HR, 1.58; 95 % CI, 1.39–1.79), independent of age, race, diabetes, and hypertension. However, that series did not report the ejection fraction of patients with coronary artery disease (CAD), or the proportion of patients that had an actual myocardial infarction [68]. A recent study assessed the risk of CHF after anthracycline therapy and found a significant association of CAD with CHF (11.8 % early CHF, 17.4 % late CHF, vs. 3.1 % in the control group ($p < 0.01$) [69]. There is to our knowledge no study that assessed whether pre-existing CAD with a normal cardiac muscle function led to a higher incidence of anthracycline-induced CHF. In the absence of decreased ejection fraction, most oncologists would give anthracyclines if essential to the treatment plan, but there might be an increased risk of CHF. On the other hand, fluoropyrimidines, such as 5-FU and capecitabine, can induce coronary vasospasm, which are most frequently asymptomatic and should be used with caution in patients with preexisting CAD [70].

Arrhythmia Management

In clinical experience, patients with a well-compensated arrhythmia typically fare well with chemotherapy. Although some arrhythmias, such as atrial fibrillation, are very frequent in the elderly, we couldn't find literature exploring their impact on chemotherapy tolerance. For patients on full anticoagulation, it might be wise to choose chemotherapy agents that minimize anemia and platelets toxicity to prevent

bleeding. Caution should be exercised with many new agents, notably kinase inhibitors, which can lead to QT prolongation. A careful review of potential drug interactions is warranted. In patients receiving arsenic trioxide, potassium levels should be maintained at 4.0 mg/dl or above, and magnesium levels should also be maintained at 1.8 mg/dl or above.

5.3.4.3 Life Expectancy and Outcomes

A retrospective study of treatment of DLBCL patients with preexisting congestive heart failure, including either systolic or diastolic heart failure, observed that elderly patients with DLBCL and baseline systolic CHF were more likely to receive non R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) based regimens, compared to patients with diastolic dysfunction and non R-CHOP treatments seemed to be better tolerated, without any obvious differences in outcome (the numbers were small) [66]. A study of lung cancer and comorbid illness [71] demonstrated that 18 % of patients with CHF received chemotherapy in comparison with 36 % of those without comorbid illness. In this study, patients with CHF had a significantly decreased survival rate (HR = 1.38, 95 % CI, 1.18–1.62) in multivariate analysis. A study of colon cancer patients reported that the use of adjuvant chemotherapy was 36.2 % in patients with heart failure compared to 64.9 % of those without heart failure [72]. Among patients with heart failure, the 5-year survival was significantly higher in patients treated with adjuvant chemotherapy (43, 95 % CI, 40–47 % vs. 30, 95 % CI, 27–34 %). A study of breast cancer patients showed that patients with early stage disease and CHF had significantly poorer survival (HR = 1.89, 95 % CI, 1.44–2.48) [73].

5.3.5 Diabetes

5.3.5.1 Diabetes and Its Incidence

With the rise in obesity in the US, the prevalence of metabolic syndrome is 40 % in patients above the age of 65 (NHANES). The prevalence of diabetes is also rapidly increasing and was 20 % for patients above the age of 65 in 2014 (CDC, accessed 1/18/2016 http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm).

In the CIRS-G and ACE 27, diabetes is rated by level of control. The Kaplan-Feinstein index was designed for diabetic patients, so diabetes is not included in the comorbidity rating. In the NIA/NCI index, the impact of diabetes is considered negligible if untreated; low if treated (medication unknown in SEER registry); and high if insulin-treated. The Charlson score attributes 1 point to diabetes without complications, and 2 points to diabetes with end-organ complications (Table 5.6).

Table 5.6 Assessment of diabetes in several comorbidity indexes

Measurement	Grade 1	Grade 2	Grade 3	Grade 4
CIRS-G	DM controlled with diet	Insulin or oral agents required	Intermediate level of severity between 2 and 4	Brittle or poorly controlled diabetes. Hx of diabetic coma in past year
Kaplan-Feinstein Index	N/A (the index was developed for diabetic patients)			
AEC-27	NIDDM controlled by oral agents	IDDM without complications; poorly controlled NIDDM	Hosp ≤6 months for keto-acidosis; diabetes with end-organ failure	–
NCI/NIA Life-Threat Model	untreated	On active management (meds unknown)	–	On insulin
Charlson comorbidity index	Diabetes without complication	Diabetes with end organ damage	–	–

(*N*)*IDDM* (non) insulin-dependent diabetes mellitus

5.3.5.2 Treatment Decision Making with Diabetes

Toxicity Issues

Many chemotherapy regimens contain high-dose steroids. Since they are given for one day only (most of the time), there is little literature on acute effects. Other regimens give it for five days. Temporary insulin regimens to control steroid-induced hyperglycemia have been proposed. In a study of 40 diabetic patients with hematologic malignancies receiving dexamethasone, intravenous or oral, for three days, a baseline and bolus regimen with insulin detemir and aspart produced better glycemic control than a sliding scale insulin regimen. Three keto-acidoses developed in the sliding scale insulin group versus 0 in the baseline/bolus group [74].

Diabetic patients have increased toxicity from chemotherapy. In a study, diabetic patients were shown to have an increased severity and a delayed recovery of paclitaxel-induced peripheral neuropathy [75] (Morena-Barrio 15). In another study, older patients treated with CHOP for NHL or docetaxel for prostate cancer were assessed for the impact of diabetes and hyperglycemia on toxicity. In both populations, hyperglycemia during chemotherapy was associated with the

occurrence of severe toxicity. For prostate cancer patients, a known diagnosis of diabetes was also associated with the occurrence of severe toxicity [76].

5.3.5.3 Life Expectancy and Outcomes

A secondary analysis of a large randomized trial showed that diabetic patients treated with a 5-FU based adjuvant chemotherapy had a shorter PFS, EFS and OS than patients without diabetes [77]. In the study on NHL and prostate cancer patients mentioned above, neither a known diagnosis of diabetes nor hyperglycemia during treatment were associated with PFS or OS [76]. Among diabetic patients, the type of treatment they receive might influence the prognosis of their cancer. Diabetic prostate cancer patients who take metformin seem to have a lesser risk of recurrence [78]. Similar results have been found in colorectal and pancreatic cancer patients [79, 80]. Diabetic breast cancer patients on metformin have a better CR rate on chemotherapy than other diabetic patients or non-diabetic patients [81]. Prospective studies are ongoing.

5.3.6 Prediction of Chemotherapy-Induced Toxicity in the Elderly

5.3.6.1 MAX2 Index

The MAX2 index [82–84] was evaluated to assess the average per patient risk for chemotherapy toxicity. Severe toxicity is defined as grade 4 hematologic toxicity and/or grade 3 and 4 non-hematologic toxicity by common terminology criteria for adverse events version 3.0.

The MAX2 index is defined as follows:

$$\frac{\text{Most frequent grade 4 hematologic toxicity} + \text{most frequent grade 3 and 4 non-hematologic toxicity}}{2}$$

The MAX 2 value for a regimen should be derived from three published studies which had at least 20 patients with a reliable reporting of toxicity. The most useful studies are the ones that provide a separate reporting of grade 4 absolute neutrophil count. Among non-hematologic toxicities, alopecia is excluded. Febrile neutropenia counts as a non-hematologic toxicity.

If ANC was not reported, ANC is extracted as follows:

$0.6 \times (\text{G3} + 4 \text{ leucopenia})$ if G4 leukopenia $< 30\,\%$
$0.8 \times (\text{G3} + 4 \text{ leucopenia})$ if G4 leukopenia is $30\,\%$ or higher

When the MAX2 index was evaluated for validation with ECOG trials, the association of the MAX2 index with the patient incidence of grade 4 hematologic

and/or grade 3 and 4 non-hematologic toxicity was highly significant for the overall group and for the elderly subgroup.

5.3.6.2 CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) Score

The CRASH score [85] was constructed in a prospective multicentric study in patients aged 70 years and older. Severe chemotherapy toxicity was defined as grade 4 hematologic toxicity or grade 3 and 4 non-hematologic toxicity according to Common Terminology Criteria for Adverse Events version 3.0. In the study, 64 % of patients experienced severe toxicity. Hematologic and non-hematologic toxicities had different predictors, and therefore the CRASH score consists of two sub-scales, which are hematologic toxicity and non-hematologic toxicity. The best predictive model for hematologic toxicity includes diastolic blood pressure (>72 mmHg; 1 point), instrumental activities of daily living (<26; 1 point), the level of LDH (equal or more than 0.75 × upper normal limit; 2 points), and toxicity of regimen. The best predictive model for non-hematologic toxicity included ECOG performance status (PS 1-2; 1 point: PS 3-4; 2 points), mini-mental status score (<30; 2 points), mini-nutritional assessment score (<28; 2 points), and toxicity of regimen. Toxicity of regimen is based on the MAX2 index. According to the level of MAX2 index, the risk of toxicity of a regimen is divided into three categories from 0 to 2.

The CRASH *score and MAX2 index are available on-line at the following website:*

https://moffitt.org/tests-treatments/treatments/senior-adult-oncology-program/senior-adult-oncology-program-tools/.

5.3.6.3 The CARG (Cancer and Aging Research Group) Score

Another toxicity risk predictive score is the CARG score [86]. This score defines severe toxicity as grade 3–5 by CTCAE. The adjustment for toxicity of chemotherapy was made by classifying it as single agents vs. combination, standard vs. reduced dose, and by tumor type. The predictors of toxicity are: creatinine clearance <34 ml/min, one or more falls in the past 6 months (3 points), age ≥72 years, GI or GU cancer, standard dose chemotherapy, polychemotherapy, hearing fair or worse, somewhat or a lot limited in walking a block (2 points), taking medications with some help/unable, limited at least some time in social activity because of physical/emotional health (1 point). A score of 0–5 is low-risk, 6–9 represents a medium risk, and a score of between 10 and 19 represents a high risk. Validation is ongoing in a CALGB trial. The score can be found online at http://www.mycarg.org/Chemo_Toxicity_Calculator.

5.4 Summary and future direction for research and practice

In conclusion, we have provided some elements to address the impact of comorbidity on survival, as well as the management of individual comorbidities in cancer treatment. More research work needs to be done, notably on the impact of multimorbidity and on other outcomes, such as relapse, progression, tolerance to chemotherapy and functional recovery or maintenance. New tools need to be developed to identify clusters of diseases with the highest impact on these outcomes.

References

1. Howlader N NA, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) SEER cancer statistics review, 1975–2012. National Cancer Institute, Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/, Apr 2015
2. Extermann M, Overcash J, Lyman GH et al (1998) Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 16:1582–1587
3. Extermann M (2000) Measuring comorbidity in older cancer patients. Eur J Cancer 36:453–471
4. Extermann M (2000) Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 35:181–200
5. Anderson G, Kerluke K (1996) Distribution of prescription drug exposures in the elderly: description and implications. J Clin Epidemiol 49:929–935
6. Kennerfalk A, Ruigomez A, Wallander MA et al (2002) Geriatric drug therapy and healthcare utilization in the United kingdom. Ann Pharmacother 36:797–803
7. Beaufrere B, Morio B (2000) Fat and protein redistribution with aging: metabolic considerations. Eur J Clin Nutr 54(Suppl 3):S48–53
8. McLean AJ, Le Couteur DG (2004) Aging biology and geriatric clinical pharmacology. Pharmacol Rev 56:163–184
9. Balducci L, Extermann M (1997) Cancer chemotherapy in the older patient: what the medical oncologist needs to know. Cancer 80:1317–1322
10. Walter LC, Schonberg MA (2014) Screening mammography in older women: a review. JAMA 311:1336–1347
11. Cho H, Klabunde CN, Yabroff KR et al (2013) Comorbidity-adjusted life expectancy: a new tool to inform recommendations for optimal screening strategies. Ann Intern Med 159:667–676
12. Jatoi I, Chen BE, Anderson WF, Rosenberg PS (2007) Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol 25:1683–1690
13. Kristjansson SR, Rønning B, Hurria A et al (2012) A comparison of two pre-operative frailty measures in older surgical cancer patients. J Geriatr Oncol 3:1–7
14. Tucci A, Ferrari S, Bottelli C et al (2009) A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer 115:4547–4553
15. Extermann M, Wedding U (2012) Comorbidity and geriatric assessment for older patients with hematologic malignancies: a review of the evidence. J Geriatr Oncol 3:49–57

16. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
17. Kaplan MH, Feinstein AR (1974) The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 27:387–404
18. Miller MD, Paradis CF, Houck PR et al (1992) Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res 41:237–248
19. Miller M, Tower A (1991) A manual of guidelines for scoring the cumulative illness rating scale for geriatrics (CIRS-G). University of Pittsburgh, Pittsburgh, PA
20. Greenfield S, Blanco DM, Elashoff RM, Ganz PA (1987) Patterns of care related to age of breast cancer patients. JAMA 257:2766–2770
21. Wallace K, Overcash J, Yoder J, Vranas P, Extermann M (2005) Influence of concomitant medications on toxicity from chemotherapy in elderly patients. Focus on cytochrome P-450 inhibition and protein binding effects. Proc Am Soc Clin Oncol 23:735s
22. Popa MA, Wallace KJ, Brunello A et al (2014) Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy. J Geriatr Oncol 5:307–314
23. Piccirillo JF, Costas I, Claybour P et al (2003) The measurement of comorbidity by Cancer Registries
24. Yancik R, Wesley MN, Ries LA et al (1998) Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. Cancer 82:2123–2134
25. Charlson ME, Sax FL, MacKenzie CR et al (1986) Assessing illness severity: does clinical judgment work? J Chronic Dis 39:439–452
26. Launay-Vacher V, Oudard S, Janus N et al (2007) Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer 110:1376–1384
27. Foundation NK (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:S1–266
28. Giannelli SV, Patel KV, Windham BG et al (2007) Magnitude of underascertainment of impaired kidney function in older adults with normal serum creatinine. J Am Geriatr Soc 55:816–823
29. Launay-Vacher V, Chatelut E, Lichtman SM et al (2007) Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations. Ann Oncol Off J Eur Soc Med Oncol/ESMO 18:1314–1321
30. Kintzel PE, Dorr RT (1995) Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. Cancer Treat Rev 21:33–64
31. Lichtman SM, Wildiers H, Launay-Vacher V et al (2007) International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer 43:14–34
32. Launay-Vacher V, Chatelut E, Lichtman SM et al (2007) Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations. Ann Oncol 18:1314–1321
33. Chen J, Wang XT, Luo PH, He QJ (2015) Effects of unidentified renal insufficiency on the safety and efficacy of chemotherapy for metastatic colorectal cancer patients: a prospective, observational study. Support Care Cancer 23:1043–1048
34. Ichioka D, Miyazaki J, Inoue T et al (2015) Impact of renal function of patients with advanced urothelial cancer on eligibility for first-line chemotherapy and treatment outcomes. Jpn J Clin Oncol 45:867–873
35. Langer CJ, Hirsh V, Ko A et al (2015) Weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: analysis of safety and efficacy in patients with renal impairment. Clin Lung Cancer 16:112–120

36. Lichtman SM, Cirrincione CT, Hurria A et al. (2016) Effect of pretreatment renal function on treatment and clinical outcomes in the adjuvant treatment of older women with breast cancer: alliance A171201, an Ancillary Study of CALGB/CTSU 49907. J Clin Oncol
37. Lee JJ, Kim J, Sehovic M, Extermann M (2015) The association of comorbidity with toxicities and clinical outcomes in elderly cancer patients treated with chemotherapy using heat maps: preliminary results. SIOG
38. Edwards BK, Noone AM, Mariotto AB et al (2014) Annual Report to the Nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 120:1290–1314
39. Gundling F, Seidl H, Schmidtler F et al (2011) Nonhepatic cancer in liver cirrhosis: a retrospective study of prevalence, complication rate after specific oncological treatment, follow-up and prognostic predictors of outcome in 354 patients with cirrhosis. Anticancer Res 31:2931–2938
40. Eklund JW, Trifilio S, Mulcahy MF (2005) Chemotherapy dosing in the setting of liver dysfunction. Oncology (Williston Park) 19:1057–1063; discussion 1063–1064, 1069
41. Verbeeck RK (2008) Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 64:1147–1161
42. Refky B, Kotb S, Fady T et al (2015) Impact of liver cirrhosis due to chronic hepatitis C viral infection on the outcome of ovarian cancer: a prospective study. BMC Cancer 15:754
43. Inghilesi AL, Gallori D, Antonuzzo L et al (2014) Predictors of survival in patients with established cirrhosis and hepatocellular carcinoma treated with sorafenib. World J Gastroenterol 20:786–794
44. Chiu J, Tang YF, Yao TJ et al (2012) The use of single-agent sorafenib in the treatment of advanced hepatocellular carcinoma patients with underlying Child-Pugh B liver cirrhosis: a retrospective analysis of efficacy, safety, and survival benefits. Cancer 118:5293–5301
45. Landgren O, Pfeiffer RM, Kristinsson SY, Bjorkholm M (2010) Survival patterns in patients with Hodgkin's lymphoma with a pre-existing hospital discharge diagnosis of autoimmune disease. J Clin Oncol 28:5081–5087
46. Gridley G, McLaughlin JK, Ekbom A et al (1993) Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst 85:307–311
47. Abu-Shakra M, Buskila D, Ehrenfeld M et al (2001) Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies. Ann Rheum Dis 60:433–441
48. Loprinzi CL, Duffy J, Ingle JN (1993) Postchemotherapy rheumatism. J Clin Oncol 11:768–770
49. Warner E, Keshavjee al N, Shupak R, Bellini A (1997) Rheumatic symptoms following adjuvant therapy for breast cancer. Am J Clin Oncol 20:322–326
50. Morales L, Pans S, Verschueren K et al (2008) Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome. J Clin Oncol 26:3147–3152
51. Vogelzang NJ, Bosl GJ, Johnson K, Kennedy BJ (1981) Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. Ann Intern Med 95:288–292
52. Papamichael D, Amft N, Slevin ML, D'Cruz D (1998) 5-Fluorouracil-induced Raynaud's phenomenon. Eur J Cancer 34:1983
53. Dumoulin FL, Leifeld L, Sauerbruch T, Spengler U (1999) Autoimmunity induced by interferon-alpha therapy for chronic viral hepatitis. Biomed Pharmacother 53:242–254
54. Ronnblom LE, Alm GV, Oberg K (1991) Autoimmune phenomena in patients with malignant carcinoid tumors during interferon-alpha treatment. Acta Oncol 30:537–540
55. Ronnblom LE, Alm GV, Oberg KE (1991) Autoimmunity after alpha-interferon therapy for malignant carcinoid tumors. Ann Intern Med 115:178–183
56. Topalian SL, Hodi FS, Brahmer JR et al (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443–2454
57. Hamid O, Robert C, Daud A et al (2013) Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 369:134–144

58. Nishino M, Sholl LM, Hodi FS et al (2015) Anti-PD-1-related pneumonitis during cancer immunotherapy. N Engl J Med 373:288–290
59. Mikuls TR, Endo JO, Puumala SE et al (2006) Prospective study of survival outcomes in Non-Hodgkin's lymphoma patients with rheumatoid arthritis. J Clin Oncol 24:1597–1602
60. Ogle KS, Swanson GM, Woods N, Azzouz F (2000) Cancer and comorbidity: redefining chronic diseases. Cancer 88:653–663
61. Hamo CE, Bloom MW (2015) Getting to the heart of the matter: an overview of cardiac toxicity related to cancer therapy. Clin Med Insights Cardiol 9:47–51
62. Ades F, Zardavas D, Pinto AC et al (2014) Cardiotoxicity of systemic agents used in breast cancer. Breast 23:317–328
63. Suter TM, Ewer MS (2013) Cancer drugs and the heart: importance and management. Eur Heart J 34:1102–1111
64. Aapro M, Bernard-Marty C, Brain EG et al (2011) Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol Off J Eur Soc Med Oncol/ESMO 22:257–267
65. Swain SM, Whaley FS, Ewer MS (2003) Congestive heart failure in patients treated with doxorubicin. Cancer 97(11):2869–2879
66. Dougoud-Chauvin V, Fradley MG, Chen L, Kim J, Walko CM, Sehovic M, Extermann M (2015) Treatment of diffuse large B-cell lymphoma and preexisting congestive heart failure: a retrospective analysis from Moffitt Cancer Center TCC database. Blood 126 (abstr 3957)
67. Aapro M, Bernard-Marty C, Brain EG et al (2011) Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol 22:257–267
68. Pinder MC, Duan Z, Goodwin JS et al (2007) Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 25:3808–3815
69. Qin A, Thompson CL, Silverman P (2015) Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin. J Cancer Surviv 9:252–259
70. Stewart T, Pavlakis N, Ward M (2010) Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. Intern Med J 40:303–307
71. Dy SM, Sharkey P, Herbert R et al (2006) Comorbid illnesses and health care utilization among Medicare beneficiaries with lung cancer. Crit Rev Oncol Hematol 59:218–225
72. Gross CP, McAvay GJ, Guo Z, Tinetti ME (2007) The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. Cancer 109:2410–2419
73. Siegelmann-Danieli N, Khandelwal V, Wood GC et al (2006) Breast cancer in elderly women: outcome as affected by age, tumor features, comorbidities, and treatment approach. Clin Breast Cancer 7:59–66
74. Gosmanov AR, Goorha S, Stelts S et al (2013) Management of hyperglycemia in diabetic patients with hematologic malignancies during dexamethasone therapy. Endocr Pract 19:231–235
75. de la Morena Barrio P, Conesa MA, Gonzalez-Billalabeitia E et al (2015) Delayed recovery and increased severity of Paclitaxel-induced peripheral neuropathy in patients with diabetes. J Natl Compr Canc Netw 13:417–423
76. Brunello A, Kapoor R, Extermann M (2011) Hyperglycemia during chemotherapy for hematologic and solid tumors is correlated with increased toxicity. Am J Clin Oncol 34:292–296
77. Meyerhardt JA, Catalano PJ, Haller DG et al (2003) Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol Off J Am Soc Clin Oncol 21:433–440
78. Hwang IC, Park SM, Shin D et al (2015) Metformin association with lower prostate cancer recurrence in type 2 diabetes: a systematic review and meta-analysis. Asian Pac J Cancer Prev 16:595–600
79. Hassabo H, Hassan M, George B, Wen S, Baladandayuthapani V, Kopetz S, Fogelman DR, Kee BK, Eng C, Garrett CR (2011) Survival advantage associated with metformin usage in patients with colorectal cancer (CRC) and type II noninsulin-dependent diabetes (NIDDM). J Clin Oncol 29 (abstr 3618)

80. Sadeghi N, Abbruzzese JL, Yeung SJ, Hassan M, Li D (2011) Effect of metformin on survival of diabetic patients with pancreatic adenocarcinoma. J Clin Oncol 29 (abstr 4063)
81. Jiralerspong S, Palla SL, Giordano SH et al (2009) Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 27:3297–3302
82. Extermann M, Bonetti M, Sledge GW et al (2004) MAX2–a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. Eur J Cancer 40:1193–1198
83. Extermann M, Chen H, Cantor AB et al (2002) Predictors of tolerance to chemotherapy in older cancer patients: a prospective pilot study. Eur J Cancer 38:1466–1473
84. Extermann M, Reich RR, Sehovic M (2015) Chemotoxicity recurrence in older patients: risk factors and effectiveness of preventive strategies-a prospective study. Cancer
85. Extermann M, Boler I, Reich RR et al (2012) Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. Cancer 118:3377–3386
86. Hurria A, Togawa K, Mohile SG et al (2011) Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol Off J Am Soc Clin Oncol 29:3457–3465

Further Reading

87. References 2–4, 14, 29, 61, 73, 84 and 85 provide a good starting point for the reader wanting to deepen further their knowledge.