Side Effects of Medical Cancer Therapy in Genitourinary Malignancies

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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. The systemic treatment of prostate cancer and renal cell carcinoma does not rely on chemotherapy, with the exception of taxane docetaxel and cabazitaxel. Prostate cancer is primarily treated by androgen deprivation, by surgical castration or LHRH analogs, or by androgen receptor pathway inhibitor enzalutamide and abiraterone acetate. Renal cell carcinoma is nowadays treated with agents targeting survival and angiogenesis pathways, including tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, axitinib, and pazopanib; anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab; mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus; and oral inhibitor of tyrosine kinases MET, VEGFR, AXL, cabozantinib. Most recently, immune checkpoint inhibitors have made their way to genitourinary cancers, revolutionizing the treatment of urothelial cancers and renal cell carcinoma.

Hormone therapies and targeted therapies don't eradicate prostate cancer and renal cell carcinoma but 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 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.

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6.1 Introduction

Genitourinary cancers are the leading forms of cancer and cancer deaths. Based on GLOBOCAN, 345,195 prostate cancers, 97,193 bladder cancers, 54,281 kidney cancers, and 18,202 testis cancers have been reported in the European Union in 2012, accounting for 36% of cancers [1]. Owing mainly to major improvements in treatment modalities, which include surgery, radiotherapy, and innovative systemic treatments, genitourinary cancers account for only 17% of cancer deaths.

Two genitourinary malignancies, prostate cancer (PCa) and renal cell carcinoma (RCC), are characterized by a limited usage of chemotherapy, in contrast to other cancer types. PCa is primarily treated by hormone therapy, mainly androgen deprivation therapy (ADT). In localized disease, ADT is used primarily in adjuvant to radiotherapy and surgery, a setting in which in dramatically increases overall survival (OS) [2]. In metastatic disease, ADT rarely controls the disease beyond a few months. Then the disease becomes castration-resistant, a stage still today uniformly lethal. The prognosis of metastatic castration-resistant prostate cancer (mCRPC) has been substantially improved by the development of several drugs: two taxane chemotherapies, docetaxel and cabazitaxel; two androgen receptor (AR) pathways inhibitors, abiraterone acetate and enzalutamide, a bone-seeking α-emitter radionuclide, Ra223; and two bone-protecting agents, zoledronic acid and denosumab [3]. In 2004, the median OS of mCRPC patients in the mitoxantrone arm of TAX-327, the docetaxel registration trial, was 16.5 months [4]. In 2017, the median OS of mCRPC treated with enzalutamide as a first line of treatment is 35.6 months [5]. The most interesting development, however, is the recent publication of four trials demonstrating an unprecedented benefit when ADT is combined with either docetaxel or abiraterone at diagnosis in newly diagnosed metastatic PCa [6–9]. CHAARTED and STAMPEDE have investigated the benefit of adding six cycles of docetaxel, at the standard dose of 75 mg/m^2 to ADT [8, 9]. The hazard ratio (HR) for OS when adding docetaxel to ADT was 0.61 and 0.78. The LATITUDE trial has tested a combination of ADT with abiraterone and prednisone 5 mg in 1199 newly diagnosed men with high-risk metastatic PCa (≥2 of Gleason score ≥ 8, visceral disease, ≥3 bone metastases) [6]. The combined treatment was shown to extend median OS from 34.7 months in the ADT group to "not reached" (HR 0.62; $P < 0.001$). The STAMPEDE trial tested the same combination in a broader group of 1917 patients; 20% were node-positive, 27% had high-risk locally advanced disease, and 5% demonstrated PSA recurrence [7]. The combined treatment significantly decreased the number of deaths from 262 with ADT alone to 184 (HR 0.63; $P < 0.001$). The 3-year survival was 83% in the combined treatment group and 76% in the ADT arm, with a HR of 0.61 for metastatic PCa.

Renal cell carcinoma (RCC), and especially its most frequent subtype, clear cell carcinoma, is an even more peculiar disease, being both radio- and chemoresistant. RCC used to be considered an immune-sensitive tumor, since the only active treatments, although of limited value, were interferon-α (Ifα) and high-dose interleukin (HD-IL2). A better understanding of the importance of the VHL/HIF hypoxia pathways has fueled the development of drug-targeting angiogenesis and survival pathways that have revolutionized the treatment of advanced RCC. Today, seven drugs have supplanted Ifα and HD-IL2: sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab, pazopanib, and axitinib. This is without counting the introduction of immune checkpoint inhibitors, nivolumab and others, whose toxicity and monitoring will be described elsewhere. Although many of these drugs confer little or no OS benefit, they have been widely accepted, and it is estimated that overall the life span of patients has been extended. But new modes of actions 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 and immune check point inhibitors, we have chosen not to cover that topic and focus on hormone therapy of PCa and targeted therapies of RCC.

6.2 Side Effects of Hormonal Treatments in Prostate Cancer

6.2.1 Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) 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 1940s [10]. ADT is primarily used alone in advanced PCa or concomitantly and adjuvant to external beam radiation therapy (EBRT), for duration ranging from 6 months to 3 years [11].

Resulting from significant improvements in the treatment advanced PCa, ADT is nowadays prescribed for longer duration, and thus the patients are much exposed to its side effects. ADT is traditionally recognized through its acute side effects, which include loss of libido and erectile dysfunction, hot flushes, fatigue, and psychological effects such as emotional instability, depression, or cognitive dysfunction [12–14]. Recently, however, more attention has been given 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 [14].

6.2.1.1 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. Hot flushes are the most common side effect, affecting by up to 80% of patients, but also among the

most bothersome and disrupting for the everyday life [13]. Hot flushes are often triggered by stress, heat, sudden changes in body position, ingestion of warm or spicy food, or smoking [13].

Management of hot flushes includes informing patients or situations or behaviors that can induce or aggravate them. Standard scale, such as the Moyad questionnaire, can be used to record frequency and severity of hit flushes [15]. 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 [12, 13, 16, 17]. 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 [18–20]. Acupuncture and phytotherapy, especially sage extracts, can eventually be recommended to patients, despite lack of definitive robust scientific evidence [21, 22].

Sexual Dysfunction

The extent of sexual dysfunction varies widely from one patient to another. The negative impact of ADT on libido and sexual function is well known, including decrease of sexual desire and impotence [23]. Patients and their partners should be informed about this, as it can cause anxiety for both, although a satisfying sexual and affective life is still possible under ADT. From a historic review of the social and intellectual performances of eunuchs, Aucoin and Wassersug suggested that, with the right cultural setting and individual motivation, ADT may actually enhance, rather than hinder, both social and sexual performance [24]. But it is important to inform and educate the patients. Walker et al. have piloted a randomized controlled trial in 27 couples to investigate the effect of an educational intervention designed to preserve couples intimacy in the face of ADT [25]. While results were not statistically significant, trends and effect sizes suggest that the educational intervention helped attenuate declines in intimacy for patients, but not for their partners. Couples who participated in the intervention were more successful at maintaining sexual activity than were couples in the control group. Traditional treatments of erectile dysfunction can be recommended in ADT-treated patients, including intracavernous injections of prostaglandins and/or phosphodiesterase-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 and meta-analysis of 16 randomized controlled trials involving 1574 PCa patients confirms that exercise has a beneficial effect on cancer-related fatigue [26]. 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 [27]. Physicians should convince patients to adopt a healthier lifestyle including a healthy diet and physical exercise. Fatigue may be further aggravated by sarcopenia (loss of skeletal muscle mass) resulting from ADT, which directly impacts on muscle strength and reduces physical activity [28].

Cognitive and Psychological Side Effects

ADT may cause psychological side effects such as reduced cognitive function (e.g., reduced concentration and memory problems), emotional instability, and even depression [13, 16]. 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. In some patients, these emotional disturbances may evolve into depression. Depression can be severe and can lead to an increased risk of suicide in the months following diagnosis of advanced PCA, probably as a mixed effect of the cancer diagnosis and the initiation of ADT [29]. Dinh et al. have conducted a survey on 78,552 men older than 65 years with localized PCa, including 43% that received ADT, using the SEER-Medicare Linked Database [30]. ADT patients, in comparison with non-ADT patients, had a higher 3-year cumulative incidences of depression (7.1% vs. 5.2%, respectively), inpatient psychiatric treatment (2.8% vs. 1.9%, respectively), and outpatient psychiatric treatment (3.4% vs. 2.5%, respectively). Adjusted Cox analyses demonstrated that patients on ADT had a 23% increased risk of depression and a 29% increased risk of inpatient psychiatric treatment. The risk of depression increases with duration of ADT, from 12% within 6 months of treatment, 26% within 7–11 months, and to 37% within 12 months of treatment. Based on this information, it is recommended to screen for patients with preexisting depression before starting them on ADT using validated scale such as the PHQ-9 questionnaire [31].

The impact on cognitive functions, dementia, and, more specifically, the specific risk of Alzheimer's disease has also grown as a concern. Wu et al. have conducted an in-depth survey on 39 PCa patients, including 10 on ADT [32]. Overall, ADT-receiving patients experienced marginally more cognitive problems than those not receiving ADT (non-ADT) even though there were no significant differences between groups in neuropsychological performance. ADT patients also experienced more declines in prospective memory and multitasking than non-ADT patients. Significant proportions of participants in both groups also experienced retrospective memory, attention and concentration, and information processing difficulties. With respect to neurobehavioral symptoms, more ADT patients experienced emotional lability and impulsivity (both aspects of disinhibition) than non-ADT patients. Nead et al. have conducted a systematic review of the literature reporting the outcome of dementia in ADT-treated PCa [33]. That analysis, which included nine studies, showed an increased risk of dementia among ADT users (HR 1.47), both all-cause

dementia (HR 1.46) and Alzheimer's disease (HR 1.25). The potential for neurocognitive deficits secondary to ADT should be discussed with patients and evaluated prospectively. The association with Alzheimer's disease has been confirmed by Jhan et al. on data from 24,360 Taiwanese PCa patients [34]. During the average 4-year follow-up period, the incidence of Alzheimer was 2.78 per 1000 person-years in the non-ADT cohort and 5.66 per 1000 person-years in the ADT cohort. After adjusting for age and all comorbidities, the combined ADT cohort was found to be 1.84 times more likely to develop Alzheimer than the non-ADT control group ($p < 0.001$).

6.2.1.2 Long-Term Adverse Events of ADT

Anemia

Hemoglobin level will drop by 10% in at least 90% of ADT patients [35]. Anemia is usually normocytic, normochromic, and due to the lack of androgen stimulation of erythroid precursors and a decrease in erythropoietin production. Anemia worsens fatigue [13]. Physicians should closely monitor hemoglobin levels in patients treated with ADT. Anemia may be aggravated by extensive invasion of the bone marrow, which frequently occurs in mCRPC patients.

Metabolic and Cardiovascular Side Effects

The relationship between ADT and an increased risk of cardiovascular disease (CVD) is intensively disputed since large epidemiological survey and prospective trials provide controversial results. In addition, two different aggravating factors coexist: an acute effect of testosterone, FSH, or GnRH flare on atherosclerotic disease and long-term consequences of metabolic changes. The first maybe a class effect of GnRH agonists, not seen with GNRH antagonists; the second probably linked to any mechanisms of testosterone suppression.

Acute Cardiotoxicity of ADT

In patients with a previous history of cardiovascular events (CVE), even short-term course of ADT may significantly increase the risk of presenting a new CVE. In 2009 already, Nanda et al. analyzed 5077 localized PCa and found that neoadjuvant 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 risk factor [36]. In the subgroup of patients with CAD, CHF, or MI, 26.3% deaths were reported in ADT-treated patients and 11.2% deaths in non-ADT-treated controls (HR 1.96; $P = 0.04$). Interestingly, the difference comes from death occurring with 2 years of initiation of treatment, suggesting an early mechanism.

This acute toxicity is pharmacology dependent, since it is less frequent with GnRH antagonists, which don't produce an initial flare of testosterone, FSL, and LH. Albertsen et al. have analyzed pooled data from 2328 patients collected in 6 phase 3 prospective randomized trials comparing the efficacy of GnRH agonists ($n = 837$) against GnRH antagonists ($n = 1491$) [37]. Noteworthy, among men with

preexisting CVD, the risk of a new CVE within 1 year of initiating therapy was significantly lower among men treated with a GnRH antagonist compared with GnRH agonists (HR 0.44; $p = 0.002$). The mechanism underlying this class effect is probably complex and involves the potential roles of testosterone flare, GnRH receptors outside the pituitary gland, and altered levels of follicle-stimulating hormone [38]. Recently, Scailteux et al. have analyzed data from 35,118 new French ADT users and found no meaningful difference in cardiovascular risk between GnRH antagonist and agonists [39]. It is fair pointing, however, that the paper included a very small number of patients treated with GnRH antagonists.

ADT-Induced Metabolic Disturbances and Cardiovascular Disease

ADT causes changes in the patient's body mass and composition [13, 28]. Suppression of testosterone causes a situation known as sarcopenic obesity, combining muscular atrophy and an increase in fatty tissue [40, 41]. 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 [42, 43]. The main cause of these metabolic changes is an increased peripheral resistance to insulin, leading to type 2 diabetes [44]. These metabolic changes may be facilitated by reduced physical activity resulting from fatigue and depression.

Impact of Metabolic Changes on Cardiovascular Events

In an observational study on 37,443 men, Keating et al. reported that ADT significantly increases the risk of diabetes (HR 1.28), coronary heart disease (CHD) (HR 1.19), myocardial infarction (MI) (HR 1.28), sudden death (HR 1.35), and stroke (HR 1.22) [45]. Combined androgen blockade and orchiectomy further increased these risks; in contrast, pure oral antiandrogen monotherapy had no detectable impact. Since that first large analyses, there has been a controversy fueled by observation made in prospective trials and in large retrospective survey (Fig. 6.1). Bosco et al. have performed a meta-analysis using observational data from eight observational studies including at least one type of ADT and a nonfatal or fatal CVD outcome [46]. The relative risk (RR) of any type of nonfatal CVD was 1.38 for men with PCa on GnRH agonists, compared with men not treated with ADT. When analyzing nonfatal ischemic heart disease only, the RR was 1.39. The RR between GnRH agonists and nonfatal or fatal myocardial infarction (1.57) or stroke (1.51) were even stronger. In contrast, systematic review and meta-analysis of randomized trials have failed to demonstrate a link between ADT and cardiovascular disease. In the meta-analysis by Nguyen et al., among 4141 patients from 8 randomized trials, CV death was not significantly different in patients receiving ADT vs. control (RR, 0.93; $P = 0.41$) [47]. ADT was not associated with excess CV death in trials of at least 3 years (long duration) of ADT (RR 0.91; P 0.34) or in trials of 6 months or less (short duration) of ADT (RR 1.00; P 0.99). Although RCTs usually provide the highest grade of evidence for the assessment of the effectiveness of therapy, these

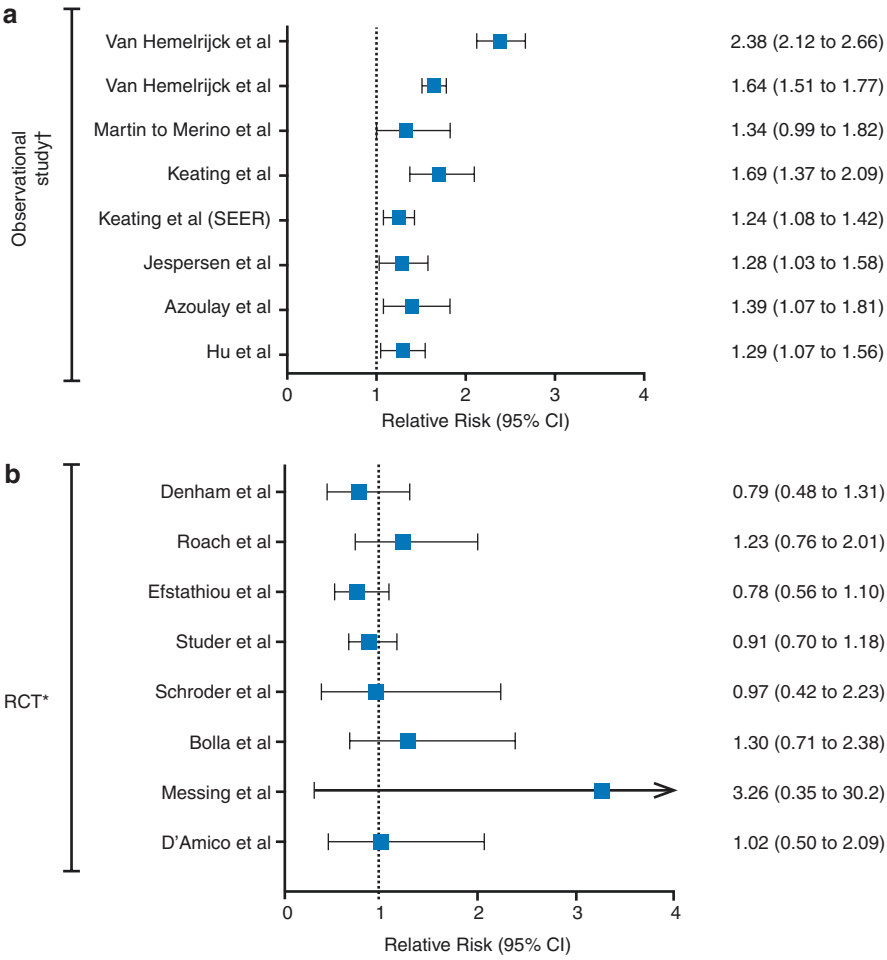

Fig. 6.1 Forest plot for the association between GnRH agonists and nonfatal or fatal myocardial infarction in epidemiological retrospective surveys (**a**, adapted from [46]) and in prospective randomized controlled trials (**b**, adapted from [47]). *RCT* randomized control trial; *SEER* surveillance, epidemiology, and end results; *CI* confidence interval; *MI* myocardial infarction; *RR* relative risk; *SEER* surveillance, epidemiology, and end results

trials tend to exclude older patients or those with a higher number of comorbidities. For instance, in the aforementioned analysis by Nguyen et al., authors highlight that given that they analyzed phase 3 RCTs, it is likely that participants had fewer comorbidities than the general population, making them less susceptible to ADT-related CV adverse effects [47].

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 [48]. 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 [49]. 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.

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 [12, 13, 15, 16, 50]. 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 [51]. 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. Studies 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 [52]. 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 [53]. The same group demonstrated that a combination of both resistance and aerobic exercise mitigates fatigue in patients treated by EBRT with or without ADT [54]. 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 [55]. 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.

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 [56]. 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 [57–59]. 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 an early bone loss [64].

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 fractures [65]. 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 fractures include race and low body mass index (<25 kg/m^2) [68]. 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 fractures, and prior osteoporosis diagnosis or treatment ($p < 0.05$) [67].

Table 6.1 Prospective studies measuring bone loss associated with ADT

Study	Treatment	BMD decrease at 12 months (%)
Eriksson 1995 [56]	Orchiectomy	Hip: 9.6 Radius: 4.5
Maillefert 1999 [60]	GnRH agonist	Hip: 3.9 Lumbar spine: 4.6
[61]	Orchiectomy GnRH agonist	Hip: 2.4
Daniell 2000 [62]	GnRH agonist	Hip: 0.6 Lumbar spine: 2.3
Higano 2004 [63]	LHRH agonist + antiandrogen	Hip: 2.7 Lumbar spine: 4.7
Mittan 2002 [64]	GnRH agonist	Hip: 3.3 Radius: 5.3

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

Study	Patients (*n*)	ADT duration (years)	Fracture risk (%)					
			All sites		Hip		Hospitalization	
			ADT	No ADT	ADT	No ADT	ADT	No ADT
Shahinian et al. [65]	50,613	1–5	19.6	12.6	4.06	2.06	5.19	2.37
Smith et al. [66]	11,661	>12	7.88[b]	6.51[b]	1.26[b]	0.98[b]		
Alibhai et al. [67]	19,079	6,7	17.2	12.7	2.6	2	8	5.7

ADT androgen deprivation therapy
[a]Rate (%) per person per year
[b]$p < 0.05$

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 the 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 [69]. When spine measurements are technically invalid, especially in the presence of bone metastases, total hip BMD should be assessed [69]. 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). 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, a score below −2.5 is osteoporotic, and a score below −2.5 with any associated fracture is considered severely osteoporotic [70]. 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 [71]. 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 cutoff duration defining long-term ADT and no recommendation on scheduling of subsequent DXA scans [11]. Similarly, physicians should be attentive to the presence of additional risk factors, as highlighted by Ebeling (Table 6.3) [70].

Table 6.3 Risk ratio for hip fracture according to risk factors adjusted for age and for 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 reference [70]

Prevention and Treatment of CTIBL in ADT-Treated Patients

Patients should be encouraged to make specific lifestyle changes: cessation of smoking, moderate alcohol and caffeine consumption, and regular weight-bearing exercises [13]. 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 1200–1500 mg, and serum levels of hydroxyvitamin D should be maintained at ≥30 ng/mL [70, 72]. If required, supplementation with cholecalciferol at doses of 800–2000 IU/day should be given. A systematic review of around 64,000 men and women showed that a daily intake of calcium (≥1200 mg) or calcium with vitamin D (≥800 IU daily) reduced the frequency of osteoporotic fractures by 12% in men and women aged ≥50 years [73]. 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 [74].

Osteoporosis is a disease that needs to be treated appropriately. The last posted version of the National Comprehensive Cancer Network (NCCN) guideline 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% [75]. 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 bisphosphonates to be studied for the prevention of CTIBL in prostate cancer in a randomized controlled trial [76]. 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 nonmetastatic prostate cancer. In the first trial, patients received zoledronic acid, 4 mg, or placebo IV every 3 months for 1 year [77]. 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 [78]. 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 [79]. 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. Injections of denosumab result in a prolonged inhibition of bone remodeling in postmenopausal women [80]. A prospective, randomized, placebo-controlled study has investigated the benefit of denosumab in the prevention of CTIBL and fractures in 1400 patients with nonmetastatic PCa receiving ADT [81]. 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.

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.

6.2.2 Modern AR Pathway Inhibitors

As mentioned in the introduction, the clinical development of abiraterone acetate and enzalutamide has profoundly reshaped the management of advanced prostate cancer [3]. Both agents are orally available, thus very convenient, and present limited toxicity which made them optimal first-line candidate in mCRPC patents. Several trials are on their way to test earlier use of these drugs. However, they both have specific side effects that the physician needs to know in order to secure long-term safety and compliance.

6.2.2.1 Abiraterone Acetate

Abiraterone acetate is an androgen synthesis inhibitor that increases OS in mCRPC patients [82, 83]. 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 [84]. This induces a reciprocal increase in the pituitary adrenocorticotropic 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 such as prednisolone, prednisone, or dexamethasone. The standard dose of corticosteroid use in mCRPC is 5 mg bid of prednisolone and prednisone. At that dose, grade 1–4 fluid retention or edema was seen in 28% of the patients (vs. 24 with prednisone 5 mg bid alone), hypokalemia in 17% (vs. 13%), and hypertension in 22% (vs. 13%), and ALT and AST increase in 12 and 11% of (vs. 5%) patients. For each of these side effects, grade 3–4 rate was ≤5% [85]. In the recently published LATITUDE and STAMPEDE studies, the dose of prednisone was lowered to 5 mg daily, which raised some concerns [6, 7]. Grade 3–4 hypokalemia was, respectively, detected in 10 and 1% patients in the abiraterone arm compared to 1 and <1% patients treated with ADT. This represents a close to fourfold increase when compared to the two mCRPC registration trials that, respectively, described an incidence of grade 3–4 hypokalemia of 2 and 4% [82, 83]. Hypertension was also more common: 37% (all grades) compared to 22% and 10%.

Patients receiving abiraterone should be monitored carefully [86]. Arterial hypertension and hypokalemia should be corrected before initiating treatment. Blood pressure, serum potassium, and symptoms of fluid retention should be measured at least monthly and corrected if required. ALT, AST, and bilirubin levels must be measured prior to starting treatment with abiraterone, and then every 2 weeks for the first 3 months of treatment, and monthly thereafter.

The indication of administering abiraterone should be carefully weighted in the following patients that constitute relative contraindications: patients with a history

of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention and patients taking CYP2D6 substrates with a narrow therapeutic index.

6.2.2.2 Enzalutamide

Enzalutamide is an oral AR receptor antagonist that was specifically engineered to overcome castration resistance in PCa cells harboring AR amplification or overexpression [87]. Enzalutamide has demonstrated significant activity in men with metastatic CRPC before or after chemotherapy [88, 89]. As for abiraterone, enzalutamide is generally very well tolerated and adapted to long-term administration. In the pre-chemotherapy registration trial, Prevail, grade $\geq$ 3 adverse events were recorded in 43% of the patients and 37% of the placebo controls. The most common grade 1–4 side effects were fatigue (36% vs. 26% in control), back pain (27% vs. 22 in control), and constipation (22% vs. 17% in control). There was more hypertension with enzalutamide (13%) than in placebo control (4%). In addition, it should be noted that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. These combinations can alter the plasma exposure of enzalutamide and should be avoided if possible. Conversely, concomitant use of strong CYP2C8 inhibitors can increase the plasma exposure to enzalutamide.

Enzalutamide belongs to a class of antiandrogens that carries a risk of seizures. This is likely related to inhibition of the γ-aminobutyric acid (GABA)-gated chloride channels by enzalutamide, which lowers the seizure threshold [89]. In the AFFIRM and PREVAIL trials, patients with a history of seizures or with other risk factors for seizures were excluded from trial entry. The risk of seizure was very low <1% in both trials.

Enzalutamide-related fatigue has been the most badly advertised side effect of enzalutamide. Investigators have conducted a pooled analysis across four double-blind, randomized, placebo- or bicalutamide-controlled trials of enzalutamide for mCRPC (AFFIRM, PREVAIL, TERRAIN, and STRIVE), representing 2051 patients in the enzalutamide arms and 1630 in the control arms [90]. Total treatment exposure was longer for enzalutamide (range 219–1294 patient-years) vs. control (range 143–560 patient-years). The unadjusted percentages of men reporting fatigue for all grades were slightly higher in enzalutamide arms (range 28–38% vs. range 20–29%). Grade 3 fatigue AEs were reported by <10% of men and in similar proportions in both arms (1–6% for ENZ vs. 1–7% for control). In all trials, younger men (<75 years) experienced less fatigue vs. older men (20–35% vs. 21–42%, respectively), regardless of treatment. Men, however, should be counseled that fatigue can manifest with enzalutamide administration.

In accordance with the summary of the European public assessment report (EPAR), no specific monitoring is recommended for patients on enzalutamide, except if it is coadministered with warfarin (CYP2C9 substrate), in which case additional INR monitoring should be conducted [91].

The indication of administering enzalutamide should be carefully weighted in the following patients that constitute relative contraindications: patients who had a

seizure, with predisposing factors for seizures, using concomitant medications that may lower the seizure threshold, or patients using CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index [91].

6.3 Side Effects of Targeted Therapies for Renal Cell Carcinoma

The treatment of RCC has been revolutionized by the development since the early 2000s of several therapies targeting the VHL/HIF pathways. These belong to four different classes of drug: tyrosine kinase inhibitors (TKIs), including sunitinib, pazopanib, sorafenib, and axitinib, anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus, and finally oral inhibitor of tyrosine kinases MET, VEGFR, AXL, cabozantinib [92–106]. Although most of these drugs have individually demonstrated limited OS benefit, 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 and usually receive multiple lines of therapy.

Because these drugs belong to specific therapeutic classes, they cause class-specific side effects that have raised new management challenges. Most of their

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

Drug	Line of treatment (previous treatment)	(*N*) patients	Control arm	PFS (months vs. control)	OS (months vs. control)
IL 2 [107]	1st	255	None	15% ORR	
Temsirolimus [99]	First (poor prognosis)	626	IF	5.5 vs. 3.1	10.9 vs. 7.3
Sunitinib [102, 103]	First	750	IF	11.0 vs. 5.0	26.4 vs. 21.8
Bevacizumab + IF [96, 108]	First	649	IF	10.2 vs. 5.4	23.3 vs. 21.3
Pazopanib [106]	First/second (cytokines)	435	Placebo	9.2 vs. 4.2	22.9 vs. 20.5
Sorafenib [94]	Second (cytokine)	903	Placebo	5.5 vs. 2.8	19.3 vs. 15.9
Everolimus [100, 101]	Second (sorafenib or sunitinib)	410	Placebo	4.9 vs. 1.9	14.8 vs. 14.4
Axitinib [101, 104]	Second (systemic)	723	Sorafenib	6.7 vs. 4.7	20.1 vs. 19.2
Cabozantinib [92, 93]	Second (antiangiogenic)	658	Everolimus	7.4 vs. 3.8	21.4 vs. 15.4

IL-2 interleukin 2; *IF* interferon; *PFS* progression-free survival; *OS* overall survival

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 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 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 [94–97, 99, 100, 102–106]. These side effects and their respective frequency are summarized in Table 6.5. The side effects of cabozantinib, most recently approved, have been treated separately [92, 93].

The impact of side effects can be greatly limited if the patient is well informed and encouraged activating preventive measures. Even mild side effects may have a great impact on a patient's quality of life that may 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 so maximize patient benefits and compliance, it is important that the physician is aware of the range of manageable side effects associated with each agent and that this information is effectively communicated to the patients.

6.3.1 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. Preneoplastic 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.
- The association of *bevacizumab* + *IFα* has been reported to cause hypertensive encephalopathy, cardiac failure, thromboembolic events, gastrointestinal perforation, and hemorrhage.
- *Pazopanib* has been reported to cause gastrointestinal perforation and gastrointestinal fistula, arterial thrombotic events, hemorrhage, and severe hepatotoxicity.

Table 6.5 Most commonly reported side effects in summary of product characteristics of European Medicines Agency for sorafenib [133], sunitinib [134], pazopanib [135], bevacizumab [136], temsirolimus [137], and everolimus [138]

	TKIs				Anti-VEGF	mTOR inhibitor	
Side Effect	Sorafenib	Sunitinib	Pazopanib	Axitinib	Bevacizumab	Temsirolimus	Everolimus
Gastrointestinal disorders							
Constipation	C	VC		VC	VC		
Diarrhea	VC	VC	VC	VC	VC	VC	VC
Dyspepsia	C	VC		C			
Dry mouth	C	C					C
Flatulence		C	C	C		C	
Glossodynia		VC		C			C
Nausea	VC	VC	VC	VC	VC	VC	VC
Oral pain		C		C		VC	C
Stomatitis	C	VC	C	VC	VC	VC	VC
Vomiting	C	VC	VC	VC	VC	VC	VC
Abdominal pain			VC		C	C	
Gastrointestinal perforation	UC				C	UC	
Acne	C	C				VC	C
Alopecia	VC	C	C	C			C
Dry skin	C	VC		VC	VC		VC
Erythema	VC	C	C	C			C
Hair color changes		VC	VC				
HFSR	VC	VC		VC	C		C
Nail disorder	C	C				VC	VC
Pruritus	VC	C	C	C		VC	
Rash	VC	VC	C	VC		VC	VC
Skin discoloration		VC			VC		
Bacterial and viral infections	UC		UC		C	VC	VC

(continued)

Table 6.5 (continued)

	TKIs				Anti-VEGF	mTOR inhibitor	
Side Effect	Sorafenib	Sunitinib	Pazopanib	Axitinib	Bevacizumab	Temsirolimus	Everolimus
Cough	C	C	C	VC		VC	VC
Dyspnea		C		VC	C	VC	VC
Epistaxis		VC	C	C	C	VC	VC
Pneumonitis	UC	C				C	VC
Pleural effusion						C	
Ejection fraction decreased	C	C	UC	C			
Hemorrhage	VC			VC		VC	VC
Hypertension	C	VC	UC	VC	VC	C	C
Deep vein thrombosis					C		
Thromboembolism					C		C
Supraventricular tachycardia					C		
Pulmonary embolism			UC		C		C
Anorexia	C	VC	C	VC	VC	VC	VC
Hypokalemia					VC	VC	C
Hyperglycemia					VC	VC	VC
Hypercholesterolemia						VC	VC
Hyperlipidemia						VC	VC
Hypophostatemia	VC		C			VC	C
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	VC				C	C
Creatinine increase	C	C				VC	C
Increase liver enzyme	UC	UC	VC	C		C	C
Proteinuria		UC	C	VC	VC	C	C

Headache	VC	VC	C	VC	C	VC	
Peripheral sensory neuropathy	C	C	UC		VC		
Depression	C	C			C	C	
Intracerebral bleeding						C	
Taste disturbance		VC	VC		VC	VC	
Arthralgia-myalgia	C	VC	C		VC	VC	C
Lacrimation increased		C			VC		
Eyelid edema		C			VC		VC
Conjunctivitis					C		VC
Eyelash discoloration			UC				
Allergic reactions	UC	UC			C		
Fatigue	VC	VC	VC	VC	VC	VC	VC
Hypothyroidism	UC	VC	C	VC			
Hyperthyroidism	UC	UC			VC		
Insomnia		C			VC	VC	VC
Mucosal inflammation		VC	C	VC	C		
Edema		VC	C		VC	VC	VC
Pyrexia						VC	VC

Frequencies are reported as very common (VC; ≥1/10 patients), common (C; ≥1/100 to <1/10 patients), or uncommon (UC; ≥1/1000 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 (adapted from reference [109])

- *Axitinib* has been reported to cause gastrointestinal perforation, hemorrhage, arterial thrombotic events, life-threatening hematologic, myocardial infarction, and asthenia.
- *Temsirolimus* has been reported to cause hypersensitivity/infusion reactions, intracerebral bleeding, bowel perforation, pericardial effusion, pneumonitis, renal failure, and delay wound healing.
- *Everolimus* has been reported to cause noninfectious pneumonitis and infections.

6.3.2 Prevention and Management of Most Common Side Effects

6.3.2.1 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 ±20% of patients receiving sorafenib and ±30% of patients treated with sunitinib and axitinib. HFSR usually appears 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 [110]. 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 a benefit in sparingly applying moisturizing cream to the hands and feet and educating patients on the first signs of HFSR [111]. Wearing soft and not constrictive shoes and even gloves is recommended. Once it is present, HSFR should be managed with topical application of corticoid-containing cream. Dose reduction, interruption, and event discontinuation may be required for grade 2–3 toxicities.

Management strategies for rash require first differentiating non-serious 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.

6.3.2.2 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 [99]. 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 [100]. 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.

6.3.2.3 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 also apply to targeted therapies in RCC [112]. 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, for example, using an 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. 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 [113]. Results from their analysis suggest that amifostine, 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 [114].

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, 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 [115], eicosapentaenoic acid diester [116], medroxyprogesterone acetate [117], and mixtures of beta-hydroxy-beta-methylbutyrate, glutamine, and arginine [118].

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. 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% [119]. 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.

6.3.2.4 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 [120]. Therefore, any underlying cause of fatigue should first be ruled out before making specific recommendations to the patient. Patients should be encouraged to conserve energy, to reschedule activities to periods of peak energy, and to stay active to promote sleep. Alternatives approaches such as stress management, relaxation techniques, and nutritional support maybe useful [121].

Hypothyroidism

Hypothyroidism is a very common side effect of sunitinib. Preexisting hypothyroidism should be detected and treated before starting sunitinib treatment, as recommended in the EU SmPC. There is no consensus on the frequency of thyroid function monitoring under treatment, although initially monthly TSH dosage are advisable [122]. It is not clear 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 [99, 100]. 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.

6.3.2.5 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-a, or pazopanib. 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 [109, 123, 124]. The routine use of home BP monitoring may be valuable in standard care for early detection and accurate assessment of BP changes [123, 124]. 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 [125–127]. 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, it 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 [128, 129]. 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 [130]. General recommendations on the prophylaxis and treatment of thrombosis in cancer patients have been produced by ASCO and the American

College of Chest Physician [131]. 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.

6.3.2.6 Wound Healing and Hemorrhage

Wound healing is one of the most important challenges that surgeons face when confronted with RCC patients treated with targeted therapies. Targeted agents have a variety of half-life, with temsirolimus at 17 h, sorafenib at 1–2 days, sunitinib at 4 days, and bevacizumab at 17 days. To minimize the effect on wound healing, most series have advocated at least a 2-week washout period for most oral TKIs. This has been especially 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. 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 [132].

Minor hemorrhagic events such as epistaxis are common in patients treated with bevacizumab, sunitinib, temsirolimus, and everolimus. 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-a. 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.

6.3.3 Toxicity of Cabozantinib

In RCC population, the experience in the safety profile of cabozantinib is limited to the results of one phase III trials [92, 93]. In the phase III METEOR trial, common AEs included diarrhea, fatigue, nausea, decreased appetite, hand–foot syndrome, and hypertension, which are also observed with other VEGFR TKIs in patients with RCC. Dose reductions occurred more frequently with cabozantinib than with everolimus (among 60% and 25%, respectively), underlining the need for careful AEs monitoring. We thus believe that the aforementioned recommendations may apply.

6.4 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 don't 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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