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Abstract

Androgens are endocrine secretions produced mainly by the testes under stimulation of the pituitary gland. They are also synthesized from the adrenal glands in both sexes and from ovaries in females. Luteinizing hormone (LH) produced by the anterior pituitary gland regulates the secretion of androgens from the Leydig cells in the testes. LH secretion is controlled by the hypothalamus via gonadotropin-releasing hormone (GnRH). Androgens play a major role in the development and maintenance of male sex characteristics. The primary and most well-known androgen is testosterone that is rapidly and irreversibly converted to dihydrotestosterone (DHT) in prostate by types 1 and 2 5α -reductase. Androgens stimulate the growth of both normal and cancerous prostate cells by binding to and activating the androgen receptor (AR), a protein that is expressed in prostate cells. Then, AR stimulates the expression of specific genes that cause prostate cells to grow. The role of androgens in prostate cancer was first established in 1941 by Huggins and Hodges. Since then androgen deprivation therapy (ADT) has become the standard of care for patients with advanced prostate cancer. In this chapter ADT and its use in prostate cancer will be discussed.

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20.1 Androgen Deprivation Therapy

ADT aims to reduce the serum testosterone to castrate level. The castrate level was defined as testosterone being less than 50 ng/dL (1.7 nmol/L), many years ago. However contemporary laboratory testing methods showed that the mean value after surgical castration is 15 ng/dL [1]. Thus, recently the level is defined as being less than 20 ng/dL (1 nmol/L). Recent definition is associated with better outcomes compared to the previous one [2–4]. However, current guidelines from the National Comprehensive Cancer Network (NCCN) recommend testosterone level of <50 ng/dL (1.7 nmol/L) as the castration level [5].

ADT can be used as adjuvant or neoadjuvant therapy in conjunction with initial treatment of patients with intermediate- or high-risk prostate cancer, patients with rising PSA after curative treatment, or patients with metastatic disease at diagnosis. It can either be used before radiotherapy in patients with large prostate to decrease the tumor volume.

ADT can be accomplished either by surgical or medical orchiectomy. The decision between two treatment options is based upon factors like the preference of the patient, cost, and availability. Combined androgen blockade (CAB) refers to the combination of any ADT with an antiandrogen.

20.2 Surgical Castration

Bilateral orchiectomy is a simple and a cheap procedure which results in rapid decrease in serum testosterone to castration levels and improvement in disease-related symptoms. Although less frequently used in North America and Europe, it is a widely used method in many countries where availability and cost of medical castration are an issue. This type of castration is permanent and irreversible; thus the psychological impact of the treatment should be discussed with the patient. Subcapsular orchiectomy is another method in which the tunica albuginea and epididymis remain intact.

20.3 Medical Castration

There are several methods of medical castration. Measuring serum PSA levels is a way to monitor patient's response to treatment.

20.3.1 Estrogens

Estrogens inhibit the release of GnRH from the hypothalamus resulting in reduction in testicular production of testosterone via suppressed LHRH secretion from the pituitary. Historically, diethylstilbestrol (DES) was used as an alternative to surgical orchiectomy. However it was shown that DES significantly increased the risk of

dying from heart disease and stroke without any survival benefit [6–7]. Due to severe side effects related to DES, estrogens are not considered as a first-line treatment.

20.3.2 Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists bind to GnRH receptors on pituitary gland resulting in initial release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This causes a subsequent increase in testosterone production from testes. However, this is a transient rise that is followed by a down-regulation of the GnRH receptors on gonadotropin-producing cells in a week. Decline in serum LH and FSH decreases testosterone levels within 3–4 weeks. Transient rise in LH 2–3 days after first injection leads to a surge in serum testosterone that lasts about a week and results in increase in the tumor growth. This is called “flare-up” phenomenon and is associated with increase in bone pain, acute bladder outlet obstruction, or other disease-related symptoms. Thus, initial treatment with GnRH is contraindicated in patients with severe urinary tract obstruction, painful bone metastases, or spinal cord compression. This can be prevented by antiandrogen treatment at least 1 week before GnRH application.

Approved GnRH analogs are leuprolide, goserelin, triptorelin, and histrelin. GnRH agonists are delivered as depot injections on a one-, two-, three-, or six-monthly periods. A castration level is usually obtained within 2–4 weeks and is reversible upon cessation of GnRH analog [8]. Klotz et al. showed that low nadir serum testosterone (<0.7 mmol/L) within the first year of ADT correlates with improved cause-specific survival (CSS) and duration of response to treatment in men being treated for biochemical failure undergoing continuous ADT [9].

20.3.3 Gonadotropin Hormone-Releasing Hormone Antagonists

GnRH antagonists immediately and reversibly bind to GnRH receptors of the anterior pituitary leading to a rapid decrease in LH, FSH, and testosterone levels without any flare. Currently approved GnRH antagonists are degarelix, abarelix, ganirelix, and cetrorelix. They are administered in parental way. They are used in the treatment where fast control of disease is needed. They do not have a long-acting depot formulation. Early GnRH antagonists led to histamine release and resulted in anaphylactic reactions [10–12].

Degarelix is the most extensively studied and widely available new GnRH antagonist with a monthly subcutaneous formulation. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at the third day. An extended follow-up has been published, suggesting a better PFS compared to monthly leuprorelin [13]. Compared with GnRH agonists, degarelix is associated with faster decline in serum testosterone and PSA levels [8]. Its definitive superiority over the LHRH analogues remains to be proven.

20.3.4 Antiandrogens

Antiandrogens (AAs) are oral compounds that competitively inhibit the binding of androgens to the androgen receptor. They can be either steroidal (e.g., cyproterone acetate (CPA), megestrol acetate, and medroxyprogesterone acetate) or nonsteroidal (e.g., bicalutamide, flutamide, and nilutamide). Nonsteroidal AAs competitively inhibit the binding of androgens to the androgen receptor. Thus serum testosterone levels are not suppressed and may even be elevated by nonsteroidal AAs. However steroidal AAs have additional progestational and antigonadotropic properties. Its application via a feedback suppression of pituitary LHRH release thus leads to a reduction of serum testosterone levels.

20.3.4.1 Steroidal AAs

They are synthetic derivatives of hydroxyprogesterone. Their main side effects are suppression of libido and erectile dysfunction. Cardiovascular toxicity and hepatotoxicity may also be seen. Cyproterone acetate (CPA), megestrol acetate, and medroxyprogesterone acetate are examples of steroidal AAs. CPA has no overall survival (OS) advantage compared to LHRH analogues [14]. Another study comparing CPA with flutamide in M1b disease did not show any difference in disease specific- and OS at a median follow-up of 8.6 years [15].

20.3.4.2 Nonsteroidal AAs

Bicalutamide is the most widely used form of nonsteroidal AAs. The licensed dosages are 50 mg or 150 mg. Bicalutamide monotherapy seems to be a tolerable regimen for patients with biochemical failure following 3D-CRT and TAD and may be effective in patients with low PSA levels at biochemical failure [16]. Its main side effects are gynecomastia and breast pain that occur in 70–80% of patients [17–19]. However it was shown that bicalutamide monotherapy increases bone mineral density, lessens fat accumulation, and has fewer bothersome side effects than treatment with a gonadotropin-releasing hormone agonist [20].

Nilutamide and flutamide are the other forms of nonsteroidal AAs. All of them have potential liver hepatotoxicity; thus liver enzymes should be regularly monitored during treatment. Nilutamide is not licensed for monotherapy. Its side effects are visual disturbances, alcohol intolerance, nausea, and specifically severe interstitial pneumonitis. Flutamide has been studied as monotherapy. The half-life of the active metabolite of flutamide is 5–6 h; thus it should be used three times daily. Its frequent side effect is diarrhea.

Castration resistance may occur during the course of the disease. Castration-resistant prostate cancer (CRPC) is considered to be mediated through two mechanisms: either androgen-receptor (AR)- dependent or AR-independent ways. Abiraterone acetate is a CYP17 inhibitor. It significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the tumor cells. It must be used together with prednisone/prednisolone (2×5 mg) to prevent drug-induced hyperaldosteronism.

Enzalutamide is another AA with a higher affinity for the androgen receptor. Nonsteroidal AAs allow transfer of ARs to the nucleus, but enzalutamide additionally blocks AR transfer leading to suppression of any possible agonist-like activity.

20.4 Combined Androgen Blockade with Antiandrogens

CAB is defined as the combination of an AA with orchiectomy or medical castration. It blocks the effect of both testicular and adrenal androgens. AAs are not indicated as monotherapy for treatment naïve patients. However it is used in conjunction with medical castration to block the side effects associated with the flare phenomenon at the initiation of ADT. Given 7–10 days before the initiation of GnRH analogue, GnRH receptors are downregulated at the hypophysis. This results in decline of LH and FSH secretion leading to decrease in testosterone to castrate level within 3–4 weeks after the start of treatment.

The decrease in testosterone production is generally reversible. However depending on the duration of ADT and patient-related other factors, it may not return to baseline levels after treatment cessation. Murthy et al. showed that after LHRHa treatment and radiotherapy, the testosterone levels of most men had recovered to normal by 18–24 weeks after the last injection [21]. D'Amico et al. showed that time to testosterone recovery was associated with a lower risk of death in men with no or minimal comorbidity [22].

Studies of short-term and long-term neoadjuvant ADT all have used CAB. To date, there are no trials comparing the use of initial CAB with AA monotherapy in nonmetastatic prostate cancer patients. Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients with Nonmetastatic Prostate Cancer (EMBARK) trial is an ongoing trial that randomizes patients to enzalutamide plus leuprolide, enzalutamide monotherapy, or leuprolide monotherapy after radical prostatectomy (RP) or radiotherapy [23].

There are two studies comparing CAB with AA monotherapy in metastatic prostatic cancer. Intergroup trial INT 0036 is a randomized, double-blind trial that compared leuprolide in combination with either placebo or flutamide in 603 patients with disseminated, previously untreated prostate cancer. Patients who received leuprolide and flutamide had a longer progression-free survival (16.5 vs. 13.9 months; $p = 0.039$) and an increase in the median length of survival (35.6 vs. 28.3 months; $p = 0.035$) with symptom control [24]. Intergroup trial INT 0105 enrolled 1387 patients with metastatic prostate cancer to orchiectomy and either flutamide or placebo. The addition of flutamide to orchiectomy does not result in a clinically significant improvement in survival. Patients who received flutamide had more toxicity compared to placebo group [25].

20.5 Intermittent Androgen Deprivation

ADT has several side effects including loss of libido, hot flashes, night sweats, psychological stress, osteoporosis, anemia, fatigue, loss of muscle mass, glucose intolerance, and changes in lipid profile. Prolonged ADT may also lead to progression of

androgen independence. The aim of intermittent androgen deprivation (IAD) is to minimize the adverse effects of continuous ADT and to delay progression of castration resistance. IAD is delivered for a period of time or until a maximal response is achieved based on PSA levels. Then ADT is withdrawn and patient is followed with PSA. ADT is initiated in case of recurrence or disease progression based on PSA levels.

20.5.1 Metastatic Disease

The intergroup trial INT 0162 was designed to assess whether intermittent therapy was noninferior to continuous therapy with respect to survival in patients with metastatic, hormone-sensitive prostate cancer. Patients with PSA level of ≥ 5 ng/mL received an LHRH analogue and an AA agent for 7 months. Patients in whom the PSA level fell to ≤ 4 ng/mL were randomly assigned to continuous or IAD [26]. ADT was reinitiated in the IAD group when the PSA level rose to 20 ng per milliliter (or returned to baseline in the case of patients who had PSA levels of < 20 ng/mL before enrollment). A total of 3040 patients were enrolled, of whom 1535 were included in the analysis. The median follow-up period was 9.8 years. Median survival was 5.8 years in the continuous-therapy group and 5.1 years in the IAD group (hazard ratio for death with intermittent therapy, 1.10; 90% confidence interval, 0.99–1.23). Intermittent therapy was associated with better erectile function and mental health ($p < 0.001$ and $p = 0.003$, respectively) at month 3 but not thereafter. There were no significant differences between the groups in the number of treatment-related high-grade adverse events. Based on these results, continuous ADT remains the standard of care in patients with metastatic prostate cancer.

20.5.2 Rising PSA

Crook et al. evaluated the noninferiority of IAD compared to continuous ADT in terms of overall survival. Patients with PSA level greater than 3 ng/mL more than 1 year after primary or salvage radiotherapy for localized prostate cancer were included. All of the 1386 enrolled patients did not have detectable metastases. Intermittent treatment was provided in 8 month cycles, with nontreatment periods determined according to the PSA level. Median follow-up was 6.9 years. Median OS was 8.8 years in the IAD group versus 9.1 years in the continuous-therapy group (hazard ratio for death, 1.02; 95% confidence interval, 0.86–1.21). There were no significant differences in adverse events. IAD provided potential benefits with respect to physical function, fatigue, and hormonal, urinary, and erectile function. This study showed that IAD was noninferior to continuous therapy with respect to OS and some quality-of-life factors improved with intermittent therapy [27].

Table 20.1 Randomized studies of radiotherapy and androgen blockade in patients with prostate cancer

Study	No of patients	Randomization	Results
RTOG 85-31 [31]	977	RT vs. RT + LHRHa (continuous)	Combined arm is better in all end points
RTOG 86-10 [32]	456	RT vs. RT + 4 month CAB	No significant difference in OS GS 2–6 patients have better OS
RTOG 92-02 [33]	1554	RT + 4 month LHRHa vs. RT + 2 year LHRHa	Long-term arm is better in all end points except OS GS 8–10 patients have better OS with long-term LHRHa
EORTC 22863 [34]	415	RT vs. RT + 3 year LHRHa	Combined arm is better in all end points

RT radiotherapy, LHRH luteinizing hormone-releasing hormone, CAB complete androgen blockade, GS Gleason score, OS overall survival

20.6 Timing of Hormonal Therapy

ADT was shown to improve OS and PFS in patients with locally advanced disease [28–30]. Table 20.1 represents the results of ADT combined with RT.

ADT was shown to be the most cost-effective therapy if started at the time that the patient developed symptomatic metastases [35]. Thus ADT should be started immediately in case of symptomatic metastases in order to palliate symptoms and prevent complications; however, controversy still exists regarding asymptomatic metastatic patients because of the lack of high-quality studies.

20.7 Hormonal Treatment Combined with Chemotherapy

Three large RCTs compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/m² every 3 weeks; within 3 months of ADT initiation) in terms of OS [36–38].

In the GETUG-15 trial [36], all patients had newly diagnosed M1 prostate cancer, either primary or after a primary treatment. After a median follow-up of 83.9 months, updated results of GETUG-15 trial were published [37]. Median OS was 62.1 months and 48.6 months for ADT plus docetaxel and ADT arms, respectively (hazard ratio [HR]: 0.88 [95% CI, 0.68–1.14]; $p = 0.3$). Median OS in ADT plus docetaxel and ADT arms, respectively, was for high-volume disease (HVD) patients 39.8 months versus 35.1 months (HR: 0.78 [95% CI, 0.56–1.09]; $p = 0.14$) for low-volume disease (LVD) patients; median was not reached and 83.4 months (HR: 1.02 [95% CI, 0.67–1.55]; $p = 0.9$). For up-front metastatic patients, OS was 52.6 months and 41.5 months, respectively (HR: 0.93 [95% CI, 0.69–1.25]; $p = 0.6$). The bPFS (HR: 0.73 [95% CI, 0.56–0.94]; $p = 0.014$) and rPFS (HR: 0.75 [95% CI,

0.58–0.97]; $p = 0.030$) were significantly longer in the ADT plus D arm. Docetaxel should not be used as part of first-line treatment for patients with non-castrate metastatic prostate cancer.

In the CHAARTED trial [38], the same inclusion criteria applied. High-volume disease was defined as either presence of visceral metastases or four or more bone metastases, with at least one outside the spine and pelvis. After a median follow-up of 28.9 months, the median overall survival was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 months vs. 44.0 months; $p < 0.001$). The median time to progression was 20.2 months in the combination group, as compared with 11.7 months in the ADT-alone group ($p < 0.001$). The rate of a prostate-specific antigen level of less than 0.2 ng/mL at 12 months was 27.7% in the combination group versus 16.8% in the ADT-alone group ($p < 0.001$). In the combination group, the rate of grade 3 or 4 febrile neutropenia was 6.2%, the rate of grade 3 or 4 infection with neutropenia was 2.3%, and the rate of grade 3 sensory neuropathy and of grade 3 motor neuropathy was 0.5%. It was concluded that ADT plus docetaxel for metastatic prostate cancer resulted in significantly longer overall survival than that with ADT alone.

STAMPEDE [39] was a multiarm, multistage trial including high-risk, locally advanced, metastatic, or recurrent prostate cancer who is starting first-line long-term hormone therapy. The standard of care (SOC) arm was ADT ($n = 1184$). The experimental arms were ADT combined with docetaxel ($n = 593$) and ADT combined with zoledronic acid ($n = 593$), and another was ADT combined with docetaxel and zoledronic acid ($n = 593$). Median follow-up was 43 months. Median overall survival was 71 months for SOC only, not reached for SOC + ZA ($p = 0.450$), 81 months for SOC + docetaxel ($p = 0.006$), and 76 months for SOC + ZA + docetaxel ($p = 0.022$). Grade 3–5 adverse events were reported for 399 (32%) patients receiving SOC, 197 (32%) receiving SOC + ZA, 288 (52%) receiving SOC + docetaxel, and 269 (52%) receiving SOC + ZA + docetaxel. Zoledronic acid showed no evidence of survival improvement, but docetaxel chemotherapy, given at the time of long-term hormone therapy initiation, showed evidence of improved survival accompanied by an increase in adverse events. Thus it was concluded that docetaxel treatment should become part of standard of care for adequately fit men commencing long-term hormone therapy. Table 20.2 summarizes the results of those four important trials.

Table 20.2 Hormonal treatment combined with chemotherapy in patients with metastatic disease

Study	No of patients	Median FU, months	Median OS, months (ADT + D vs. ADT)	p value
Gravis et al. [36]	385	50	58.9 vs. 54.2	0.955
Gravis et al. [37]	385	82.9	60.9 vs. 46.5	0.44
Sweeney et al. [38]	790	28.9	57.6 vs. 44	<0.001
STAMPEDE trial [39]	SOC 1184	43	81 vs. 71	0.006
	D 593		76 vs. NR	0.022
	D + ZA 593		60 vs. 45	0.005

ADT androgen deprivation therapy, D docetaxel, FU follow-up, NR not reported, ZA zoledronic acid, OS overall survival

20.8 Side Effects of Hormonal Treatment

ADT has been shown to improve survival when used with radiation for patients with intermediate- and high-risk disease and locally advanced and node-positive disease. However it may cause side effects on bone, metabolic, cardiovascular, sexual, and cognitive health as well as body composition that negatively affect quality of life of patients.

20.8.1 Osteoporosis and Bone Fractures

ADT decreases bone mineral density (BMD). It was shown that ADT significantly increases risk for any clinical fracture, hip fractures, and vertebral fractures in men with prostate cancer, and the duration of treatment affects the onset of complications [40, 41]. Calcium (1000–1200 mg daily from diet and supplements) and vitamin D (800–1000 IU daily) are recommended to reduce the ADT side effects [42]. Osteoclast inhibition with either bisphosphonates or denosumab is recommended for men with bone metastases. Osteoclast inhibition can decrease bone turnover and increase bone mineral density in men receiving ADT [43].

20.8.2 Cardiovascular Events

The first report identifying a possible CV risk with LHRH agonists was by Keating et al., who analyzed the Surveillance, Epidemiology, and End Results (SEER) Medicare data of 73,196 men with locoregional prostate cancer [44]. A significantly increased risk of coronary heart disease, myocardial infarction, and sudden cardiac death was reported for men receiving an LHRH agonist compared with those not undergoing ADT. Prospective clinical trials have demonstrated that ADT may increase cardiovascular disease risk by increasing body weight, reducing insulin sensitivity, and/or resulting in dyslipidemia. In a prospective 12-month study of 40 men with prostate cancer, ADT increased serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides by 9%, 7%, 11%, and 27%, respectively [45].

It is advisable that patients in whom ADT is initiated be on periodic follow-up that includes assessment of blood pressure, lipid profile, and glucose level. Some of the effects of ADT occur within the first 3 months of treatment; thus it may be reasonable for an initial follow-up evaluation to occur within 3–6 months after initiation of therapy. There are no data to guide at what intervals periodic further follow-up should occur, and this is left to the discretion of the physician initiating ADT and to the patient's primary care physician. Prudence and good medical care dictate that patients with cardiac disease receive appropriate secondary preventive measures as recommended by the American Heart Association and other expert organizations, including, when appropriate, lipid-lowering therapy, antihypertensive therapy, glucose-lowering therapy, and antiplatelet therapy [46].

20.8.3 Sexual Dysfunction

Since the incidence of prostate cancer is higher among older patients, at least one-third of men have sexual problems at diagnosis. However, most of the patients receiving continuous ADT who are potent prior to therapy develop sexual dysfunction. Loss of libido in patients receiving LHRH agonists usually develops within the first months followed by erectile dysfunction [47]. Erections do not recover in about one-half of men, even if ADT is discontinued. Although intermittent ADT allows some recovery of sexual function, serum testosterone requires 9–12 months off ADT to recover [48].

20.8.4 Vasomotor Symptoms

The most common symptom associated with ADT is hot flashes. Hot flashes are usually described as an intense sensation of warmth in the face and upper part of the body which seems similar to postmenopausal symptoms in women. The treatment should be decided depending on the degree of symptoms and potential side effects of the treatment. Megestrol and estrogen appear substantially more effective than venlafaxine. However, estrogen is associated with breast symptoms, megestrol is associated with increased appetite and weight, and venlafaxine is associated with dry mouth. It is recommended to start with a selective serotonin reuptake inhibitor and reserve hormonal treatment (estrogen, megestrol) for refractory cases.

20.8.5 Body Composition and Metabolism

A prospective study of 32 men receiving 12 months of GnRH agonists found a 2.4% weight gain, 9.4% increase in body fat percentage, and 2.7% decrease in lean body mass at 12 months [49]. Another prospective study of 25 patients without diabetes found that 12 weeks of combined androgen blockade resulted in a 12.8% decrease in insulin sensitivity and a 25.9% increase in fasting plasma insulin [50]. Basaria et al. conducted a cross-sectional study among 53 men, including 18 men with PCa who received ADT for at least 12 months prior to the onset of the study (the ADT group), 17 age-matched men with nonmetastatic PCa who had undergone prostatectomy and/or received radiotherapy and who were not receiving ADT (the non-ADT group), and 18 age-matched controls (the control group). It was shown that men on long-term ADT had significantly higher fasting glucose (131 vs. 103; $p < 0.01$) and greater insulin resistance (17 vs. 6; $p < 0.01$) and that 44% of the men on ADT had fasting glucose in the diabetic range (>126 mg/dL) compared with 11–12% for the controls [51].

Per the Adult Treatment Panel III (ATP III) guidelines, the diagnosis of metabolic syndrome requires the presence of three of the following five criteria: (1) serum triglycerides ≥ 150 mg/dL, (2) high-density lipoprotein (HDL) < 40 mg/dL, (3) fasting serum glucose >110 mg/dL, (4) waist circumference ≥ 40 inches, and (5)

blood pressure $\geq 130/85$ [52]. As noted earlier, patients receiving ADT are at risk for higher fasting serum glucose and increased waist size due to central weight gain. Triglycerides have also been reported to rise by 26.5% ($\pm 10\%$; $p = 0.01$) with 1 year of ADT [49]. There are currently no specific recommendations regarding the management of insulin resistance and lipid increases for men on ADT.

20.8.6 Gynecomastia

Gynecomastia and breast pain may be seen in patients on ADT. The incidence of gynecomastia was reported to be as high as 85% in patients receiving high-dose 150 mg daily bicalutamide antiandrogen monotherapy [53]. However, the incidence is lower (13–22%) in men receiving combined androgen blockade [54]. Di Lorenzo et al. investigated the role of tamoxifen and radiotherapy for the prevention and treatment of gynecomastia and breast pain during adjuvant bicalutamide monotherapy after RP in patients with prostate cancer [55]. It was shown that gynecomastia and breast pain induced by bicalutamide monotherapy after RP can be prevented and treated. Tamoxifen has been shown to be more effective and safe than RT (12 Gy) in this setting, and QOL and sexual function are not negatively influenced by these two treatment options. Ozen et al. investigated the efficacy of prophylactic radiotherapy for gynecomastia/breast pain induced by 150 mg bicalutamide in a prospective, randomized, multi-institutional trial [56]. After definitive treatment for localized prostate cancer, 125 patients were randomized to 12 Gy radiotherapy before bicalutamide as prophylactic radiotherapy or bicalutamide only for nonprophylactic radiotherapy. With a follow-up of 12 months, the gynecomastia rate was 15.8% in the prophylactic group and 50.8% in the nonprophylactic group ($p < 0.001$). Although prophylactic breast irradiation seemed to decrease the gynecomastia rate in patients on 150 mg bicalutamide, not all patients need prophylaxis since only 52% were significantly bothered by gynecomastia. Thus, it was recommended to select patients who need prophylactic radiation based on individual assessment.

20.8.7 Other

Fatigue is another side effect of ADT. The main strategy to reduce fatigue is exercise. Anemia and reduction in penile and testis size may be seen. Hypogonadism has been linked to cognitive declines in patients on ADT [57].

20.9 Follow-Up During Hormonal Treatment

EAU-ESTRO recommends follow-up of 3–6 month intervals. As a minimum, tests should include serum PSA measurement, physical examination, serum testosterone, and careful evaluation of symptoms to assess the treatment response and side effects. Patients should be warned about the signs of metastatic situations like occult cord

compression, urinary tract complications/obstruction signs, and bone pain. Routine imaging is not indicated asymptomatic in patients. However, new-onset bone pain requires a bone scan, as does PSA progression suggesting CRPC status, if a treatment modification is considered [43].

The measurement of serum testosterone levels should be a part of follow-up of patients on LHRH therapy. Although timing of measurements is not clearly defined, a 3–6 month assessment of the testosterone level might be performed to evaluate the effectiveness of treatment and to ensure that the castration level is being maintained. If it is not achieved, switching to another type of treatment modality can be attempted. In patients with rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

Long-term ADT reduces bone mineral density (BMD) and increases the risk of fractures [58]. In the absence of associated risk factors, it is recommended that BMD and serum vitamin D and calcium levels should be measured every 2 years [59]. Patients should be screened for the development of alterations in lipid profiles and decreased insulin sensitivity [60]. ADT may increase the risk of diabetes and cardiovascular disease [61]. Patients should be given advice on modifying their lifestyle (e.g., diet, exercise, smoking cessation) and should be treated for any existing conditions, such as diabetes, hyperlipidemia, and/or hypertension. Furthermore, the risk–benefit ratio of ADT must be considered for patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

20.10 Castration-Resistant Prostate Cancer

CRPC is defined as castrate serum testosterone <50 ng/dl plus either biochemical or radiological progression. Biochemical progression is defined as three consecutive rises in PSA 1 week apart, resulting in two 50% increases over the nadir, and PSA >2 ng/mL. Radiological progression is defined as the appearance of new lesions, either two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumors.

20.10.1 First-Line Treatment in Metastatic Castration-Resistant Prostate Cancer

Abiraterone was evaluated in 1088 chemo-naïve metastatic CRPC patients in the phase 3 trial. Patients were randomized to abiraterone acetate or placebo, both combined with prednisone [62]. After a median follow-up of 22.2 months, there was significant improvement of radiographic PFS (median: 16.5 vs. 8.2 months; HR: 0.52; $p < 0.001$). At the final analysis, with a median follow-up of 49.2 months, the OS end point was significantly improved (34.7 vs. 30.3 months; HR: 0.81; 95% CI, 0.70–0.93; $p = 0.0033$) [63].

PREVAIL is a randomized phase 3 trial that included a similar patient population and compared enzalutamide with placebo. It was conducted in 1717 chemo-naïve

mCRPC patients and showed significant improvement in both radiographic PFS (HR: 0.186; 95% CI, 0.15–0.23; $p < 0.0001$) and OS (HR: 0.706; 95% CI, 0.6–0.84; $p < 0.001$). The most common clinically relevant AEs were fatigue and hypertension. The results showed that enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer [64].

In a phase 2 randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic CRPC, 125 patients were randomly assigned in a multicenter trial of vaccination series. After a median follow-up of 34 months, median survival was 25.8 months in the sipuleucel-T group compared with 21.7 months in the placebo group ($p = 0.03$). PFS was similar in both groups and treatment tolerance was very good [65].

Tannock et al. compared docetaxel plus prednisone with mitoxantrone plus prednisone in 1006 men with metastatic hormone-refractory prostate cancer. The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the group given docetaxel every 3 weeks, and 17.4 months in the group given weekly docetaxel. Among these three groups, 32%, 45%, and 48% of men, respectively, had at least a 50% decrease in the serum PSA level ($p < 0.001$ for both comparisons with mitoxantrone); 22%, 35% ($p = 0.01$), and 31% ($p = 0.08$) had predefined reductions in pain; and 13%, 22% ($p = 0.009$), and 23% ($p = 0.005$) had improvements in the quality of life. Adverse events were also more common in the groups that received docetaxel [66].

ALSYMPCA is a phase 3 trial that enrolled 921 patients with symptomatic mCRPC who failed or were unfit for docetaxel. Patients were randomized to six injections of 50 kBq/kg Ra 223, every 4 weeks, or placebo, plus standard of care. Ra 223, an alpha emitter, significantly improved median OS by 3.6 months (HR: 0.70; $p < 0.001$) [67]. Ra-223 treatment was associated with prolonged time to first skeletal event and improvement in pain scores and QoL. Radium-223 was associated with low myelosuppression rates and fewer adverse events. The updated analysis of ALSYMPCA trial showed that Ra-223 was effective and safe regardless of previous docetaxel use [68].

20.10.2 Second-Line Treatment Options and Beyond in Metastatic Castration-Resistant Prostate Cancer

Cabazitaxel is a form of taxane that has an activity in docetaxel-resistant cancers. TROPIC trial is a large prospective randomized phase 3 trial comparing cabazitaxel plus prednisone versus mitoxantrone plus prednisone in 755 patients with mCRPC who had progressed after or during docetaxel-based chemotherapy [69]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) plus prednisone (10 mg/dL), respectively. OS was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months; $p < 0.0001$). Treatment-associated World Health Organization grade 3–4 AEs developed significantly more often in the cabazitaxel arm, particularly hematological toxicity (68.2% vs. 47.3%; $p < 0.0002$).

but also nonhematological toxicity (57.4% vs. 39.8%; $p < 0.0002$). This drug should be administered preferably with prophylactic granulocyte colony-stimulating factor and by physicians with expertise in handling neutropenia and sepsis [70].

AFFIRM is a trial including 1199 mCRPC patients with randomization in a 2:1 fashion to enzalutamide or placebo [71]. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. After a median follow-up of 14.4 months, median survival in the enzalutamide group was 18.4 months compared with 13.6 months in the placebo arm (HR: 0.63; $p < 0.001$). The benefit was observed regardless of age, baseline pain intensity, and type of progression. All secondary objectives including soft tissue response, QoL response rate, and time to PSA progression or objective progression were in favor of enzalutamide. Rates of fatigue, diarrhea, and hot flashes were higher in the enzalutamide group. Seizures were reported in five patients (0.6%) receiving enzalutamide compared to none in the placebo group.

Conclusion

ADT has become the standard of care for patients with advanced prostate cancer. ADT aims to reduce the serum testosterone to castrate level. The contemporary laboratory testing methods showed that the mean value after surgical castration is 15 ng/dL. Thus, recently the level is defined as being less than 20 ng/dL (1 nmol/L). Recent definition is associated with better outcomes compared to the previous one. ADT can be used as adjuvant or neoadjuvant therapy in conjunction with initial treatment of patients with intermediate or high-risk prostate cancer, patients with rising PSA after curative treatment, or patients with metastatic disease at diagnosis. It can either be used before radiotherapy in patients with large prostate to decrease the tumor volume.

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