Androgen Deprivation Therapy for Prostate Cancer: Adverse Effects

Subjects: Allergy

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Prostate cancer is the second leading cause of cancer death in men in the United States. Androgen deprivation therapy (ADT) is currently the primary treatment for metastatic prostate cancer, and some studies have shown that the use of anti-androgen drugs is related to a reduction in cognitive function, mood changes, diminished quality of life, dementia, and possibly Alzheimer's disease. ADT has potential physiological effects such as a reduction in white matter integrity and a negative impact on hypothalamic functions due to the lowering of testosterone levels or the blockade of downstream androgen receptor signaling by first- and second-generation anti-androgen drugs.

Keywords: androgen deprivation therapy ; cognitive function ; prostate cancer

1. Introduction

The treatment for hormone-sensitive metastatic prostate cancer commonly entails the use of androgen deprivation therapy (ADT), which, by suppressing or blocking testosterone, deprives the tumor of a key factor driving its growth . Since approximately 11.6% of males will be affected by prostate cancer in their lifetime, the number of men undergoing this treatment is large and growing [1][2].

Since testosterone plays an important role in cognition and mood, ADT can impact these key characteristics and, therefore, degrade quality of life [3]. These side effects of ADT pose a challenge, particularly because they may reduce adherence to life-prolonging medical therapies [4]. This is a conundrum for the healthcare provider and patients because multiple cooperative studies including randomized clinical trials have shown the efficacy of hormonal therapy in patients with metastatic disease to improve overall survival and decrease skeletal-related events [5][6].

2. Indications for ADT

ADT is the primary treatment for metastatic prostate cancer, with the benefit of improved survival [7][8][9]. It may also be used short term in patients with localized disease considered at risk for progression [10].

3. ADT Medications and Their Mechanism of Action

Androgens, secreted primarily by the testicles in men, behave as neuromodulators by activating neuronal androgen receptors. The activation of these receptors then drives changes in gene transcription that affect brain function [11][12]. Androgens support optimal cognitive function, specifically memory [13][14][15].

ADT utilizes androgen receptor antagonists and second-generation anti-androgens to prevent the translocation of androgen receptors to the nucleus [16]. First-generation anti-androgens such as flutamide and nialamide solely prevent the translocation of androgen receptors to the nucleus and downstream signaling, while second-generation anti-androgens such as enzalutamide and abiraterone have their own mechanisms of action [17]. Apalutamide, darolutamide, and enzalutamide act as anti-androgens by inhibiting both androgen binding to its receptor and the translocation of the receptor from cytoplasm to nucleus and have much greater pharmacologic potency than first-generation drugs (**Figure 1**) [18]. They also impede the binding of the androgen receptor to androgen response elements on DNA, thus inhibiting DNA transactivation. Abiraterone is an irreversible inhibitor of the enzyme cytochrome P17 (CYP17), which has both 17α-hydroxylase and C17,20-lyase activity and catalyzes multiple steps in androgen biosynthesis (**Figure 2**) [19]. Either abiraterone or enzalutamide as second-generation anti-androgens can reduce tumor burden, prolong life, and relieve symptoms, but resistance to the drugs eventually allows disease progression [20][21].

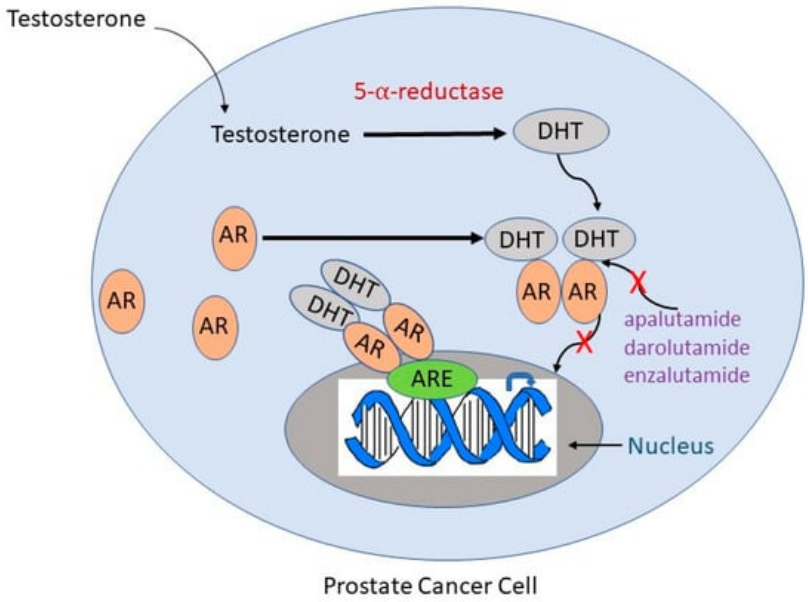

Figure 1. Mechanisms of action of anti-androgen drugs frequently used in ADT. Testosterone is converted to DHT by 5-α-reductase. DHT binds to the AR, causing a conformational change in the receptor that leads to its homodimerization and translocation to the nucleus. In the nucleus, the AR binds to the ARE and acts as a transcription factor to signal downstream targets. Second-generation anti-androgens such as apalutamide, darolutamide, and enzalutamide competitively suppress binding of androgens to the AR (indicated by a red "X") and inhibit AR translocation to the nucleus (indicated by a red "X"). DHT, dihydrotestosterone; AR, androgen receptor; ARE, androgen response element.

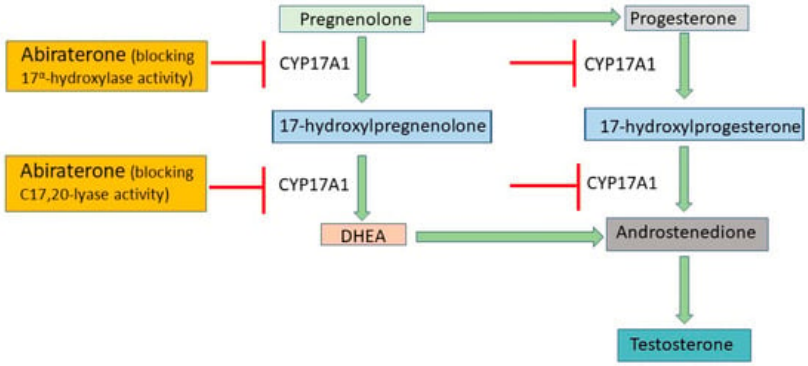

Figure 2. Mechanisms of action of abiraterone. Abiraterone blocks the activity of CYP17A1, a key enzyme in the production of testosterone. By inhibiting CYP17A1, it prevents conversion of pregnenolone to DHEA and progesterone to androstenedione, resulting in decreased testosterone biosynthesis. CYP17A1, cytochrome P450, family 17, subfamily A, polypeptide 1; DHEA, dehydroepiandrosterone.

4. ADT Risks and Side Effects

4.1. Overview of Side Effects

ADT comes with a variety of side effects and increased risks [22]. Androgen signaling is essential for maintaining homeostasis in multiple organ systems, and ADT treatment relies on disrupting this pathway, leading inevitably to a number of negative side effects. In addition, quality of life is affected by ADT due to other common consequences of androgen deficit. These can include hot flushes, sexual dysfunction, bone loss, and heightened cardiovascular risk [23][24][25][26].

4.2. Hot Flushes

Hot flushes, also referred to as hot flashes, are characterized by a sudden and intense sensation of heat, particularly in the face, throat, and extremities. The body reacts to this perceived temperature rise, causing cutaneous vasodilation, excessive sweating, rapid heartbeat, chills, night sweats, and feelings of anxiety. These physiological responses are often accompanied by redness in the face and neck [27]. These episodes can be triggered by hormonal changes, specific medications, or underlying medical conditions. The intensity and duration of hot flushes can differ from one person to another, and they may affect daily routines and sleep patterns [28]. Sleep disturbance brought on by hot flushes can adversely affect cognitive function [29].

In a randomized, double-blind study involving 208 patients with androgen-dependent prostate cancer, the quality of life of participants was assessed after a 3- to 4-month run-in phase with ADT followed by the randomization of sipuleucel-T cellular immunotherapy or control at a 2:1 ratio. During the first week, the most frequently observed symptoms were hot flashes/sweats (87.3%), reduced sexual desire (66.1%), and reduced sexual function (50.9%). However, after the discontinuation of ADT during the randomized phase, the occurrence of these symptoms decreased [30]. In comparison, Kaplan et al. found that hot flashes were reported in only 13 out of 62 patients receiving enzalutamide and radiotherapy. Those who exhibited hot flushes reported very mild symptoms [31]. In a retrospective, medical chart review study, Hussain et al. found that, in a subset of prostate cancer patients treated with apalutamide or enzalutamide and experiencing adverse events, the incidence of hot flushes was 13.9% [32]. In other studies, hot flushes were typically reported in about 50% of men undergoing ADT and were often considered the most bothersome side effect [33]. The mechanism of hot flushes in men undergoing ADT remains unclear. It is suggested that, following GnRH agonists, there is a rapid decline in serum luteinizing hormone and follicle-stimulating hormone levels, triggering the release of hypothalamic catecholamines. These catecholamines may potentially overwhelm the thermoregulation center in the hypothalamus, resulting in a dysregulated response to temperature changes [34]. The body's thermoregulation system appears to be influenced by androgens. When individuals experience a significant reduction in hormone levels, as is the case with men taking androgen antagonists, the body responds in a manner that induces hot flushes.

Several treatment strategies have been applied to alleviate the intensity of hot flushes. Small doses of estrogen aim to restore the balance of hormone levels and mitigate symptoms of ADT [24][35]. Adverse effects such as gynecomastia are the downside of this treatment [36]. Steroidal progestins, such as megestrol acetate, cyproterone acetate, and medroxyprogesterone, are also associated with the reduction in hot flushes [37]. However, steroidal progestins are linked to a wide range of side effects, including nausea, weight gain, muscle spasms, depression, insomnia, and headaches [36][38]. Clonidine, an alpha-2 receptor agonist, may provide relief of hot flushes by impacting the thermoregulatory center, but its effectiveness is uncertain [36][37][38]. Non-hormonal treatments may also include selective serotonin reuptake inhibitors (SSRIs) and antidepressants may be helpful [37].

4.3. Sexual Dysfunction

Men who have been prescribed and take androgen antagonists experience a wide array of sexual side effects. Understanding the primary factors impacting sexual function in men is challenging, given the multitude of psychological, environmental, and physiological aspects that influence sexual performance. Nevertheless, well-established evidence demonstrates a significant role for testosterone in influencing sexual drive and, as a result, low testosterone levels are linked to low libido and impaired erectile and orgasmic functions [39][40].

The corpora cavernosa, two cylindrical structures running along the length of the penis and responsible for erection, contain androgen receptors that govern the key biochemical pathways essential for achieving an erection [41]. Achieving an erection is a multifaceted physiological event that begins when the nervous system releases nitric oxide (NO) and other neuroendocrine factors, which promote the relaxation of smooth muscle cells in the penile arteries and corpora cavernosa, causing increased blood flow to the penis. The veins that typically drain blood from the penis become compressed, aiding in maintaining the erection and ensuring turgidity. The initial release of NO is partly facilitated by testosterone [42]. Reduced testosterone can induce endothelial dysfunction, a condition where the endothelium, the inner lining of blood vessels, loses its ability to regulate vascular tone and function properly. Low testosterone impacts NO levels by reducing NO synthase expression and activity and increasing asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of NO formation. Furthermore, testosterone may influence the endothelial repair system by modulating the proliferation and migration of endothelial progenitor cells [43]. Consequently, low levels of testosterone can make it increasingly challenging to initiate and sustain an erection. While the exact mechanism of how testosterone impacts libido is unclear, the association between reduced libido and low testosterone levels has been well documented [44]. Sexual dysfunction is a potential outcome across almost all treatment options for prostate cancer, but ADT may exacerbate these symptoms even further. These findings have raised concerns about the effects of ADT, not only on the health-related quality of life of patients, but also on the overall well-being of their intimate relationships [45]. The intensity of these symptoms can be so debilitating and disturbing that it is associated with a lack of adherence to treatment, despite a heightened risk of relapse or mortality [46]. When undergoing ADT, it becomes evident that the removal of testosterone from the body not only impairs erectile and orgasmic functions but also diminishes the desire to participate in sexual activities.

4.4. Bone Density

ADT is associated with reduced bone mineral density (BMD) and an increased risk of fractures [47][48]. Testosterone plays a crucial role in maintaining the strength and density of bones by regulating the balance between bone formation and resorption. ADT decreases testosterone levels and disrupts this balance, leading to bone loss with skeletal fragility. Maintaining the proper balance of receptor activator of nuclear factor k-B ligand (RANKL) is crucial for the equilibrium between bone formation by osteoblasts and bone resorption by osteoclasts. Increased RANKL levels cause increased bone resorption, leading to a decrease in BMD and the development of osteoporosis [49][50][51].

BMD decline with ADT is not preventable, but adequate calcium and vitamin D intakes are important. Osteoporosis risk factors that can be modified include avoiding tobacco and limiting alcohol consumption [48]. Pharmacological approaches aimed at preserving or enhancing bone health include medications that inhibit bone resorption, such as bisphosphonates and denosumab [52].

4.5. Cardiovascular Effects of ADT

ADT substantially heightens cardiovascular event risk as well as the risk for hypertension and arrhythmia [3][53][54]. ADT has been associated with an increased risk of developing metabolic conditions that contribute to cardiovascular risk such as insulin resistance, dyslipidemia, diabetes, and metabolic syndrome [55][56]. Of considerable significance, cardiovascular disease stands as the primary cause of mortality among individuals with prostate cancer [57]. Reducing the cardiovascular toxicity of ADT is generally approached by controlling modifiable risk factors such as blood pressure and lipid profile while encouraging a healthy diet, physical activity, and the avoidance of tobacco and excess alcohol consumption [58]. The etiology of cardiovascular disease in men with prostate cancer continues to be a subject of ongoing research [59][60].

4.6. ADT and Cognition

Those with prostate cancer are generally older, with most above age 65 and are therefore in the age category more likely to be diagnosed with dementia from Alzheimer's disease and other etiologies. In addition, there is more and more evidence supporting a relationship between ADT and cognitive issues while prostate cancer itself does not impair cognition. Common complaints of those experiencing cognitive issues on ADT include difficulty with memory, concentration and focus. The causality of this association has not been established, but the field is moving forward and the problem merits attention because it has a profound effect on quality of life. There is a need for treatment to address the cognitive complaints of those living with prostate cancer and receiving ADT that is prompting research into new approaches.

References

1. Taitt, H.E. Global Trends and Prostate Cancer: A Review of Incidence, Detection, and Mortality as Influenced by Race, Ethnicity, and Geographic Location. Am. J. Mens Health 2018, 12, 1807–1823.
2. Wang, L.; Lu, B.; He, M.; Wang, Y.; Wang, Z.; Du, L. Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. Front. Public Health 2022, 10, 811044.
3. Nguyen, P.L.; Alibhai, S.M.; Basaria, S.; D'Amico, A.V.; Kantoff, P.W.; Keating, N.L.; Penson, D.F.; Rosario, D.J.; Tombal, B.; Smith, M.R. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur. Urol. 2015, 67, 825–836.
4. Zitzmann, M. Testosterone, mood, behaviour and quality of life. Andrology 2020, 8, 1598–1605.
5. Bennett, C.L.; Tosteson, T.D.; Schmitt, B.; Weinberg, P.D.; Ernstoff, M.S.; Ross, S.D. Maximum androgen-blockade with medical or surgical castration in advanced prostate cancer: A meta-analysis of nine published randomized controlled trials and 4128 patients using flutamide. Prostate Cancer Prostatic Dis. 1999, 2, 4–8.
6. Mandel, P.; Hoeh, B.; Wenzel, M.; Preisser, F.; Tian, Z.; Tilki, D.; Steuber, T.; Karakiewicz, P.I.; Chun, F.K.H. Triplet or Doublet Therapy in Metastatic Hormone-sensitive Prostate Cancer Patients: A Systematic Review and Network Meta-analysis. Eur. Urol. Focus 2023, 9, 96–105.
7. Hall, M.E.; Huelster, H.L.; Luckenbaugh, A.N.; Laviana, A.A.; Keegan, K.A.; Klaassen, Z.; Moses, K.A.; Wallis, C.J.D. Metastatic hormone-sensitive prostate cancer: Current perspective on the evolving therapeutic landscape. Onco. Targets Ther. 2020, 13, 3571–3581.
8. Cornford, P.; van den Bergh, R.C.N.; Briers, E.; Van den Broeck, T.; Cumberbatch, M.G.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part

II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur. Urol. 2021, 79, 263–282.

9. Armstrong, A.J.; Azad, A.A.; Iguchi, T.; Szmulewitz, R.Z.; Petrylak, D.P.; Holzbeierlein, J.; Villers, A.; Alcaraz, A.; Alekseev, B.; Shore, N.D.; et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. J. Clin. Oncol. 2022, 40, 1616–1622.
10. Mell, L.K.; Pugh, S.L.; Jones, C.U.; Nelson, T.J.; Zakeri, K.; Rose, B.S.; Zeitzer, K.L.; Gore, E.M.; Bahary, J.P.; Souhami, L.; et al. Effects of Androgen Deprivation Therapy on Prostate Cancer Outcomes According to Competing Event Risk: Secondary Analysis of a Phase 3 Randomised Trial. Eur. Urol. 2023, in press.
11. Tobiansky, D.J.; Wallin-Miller, K.G.; Floresco, S.B.; Wood, R.I.; Soma, K.K. Androgen Regulation of the Mesocorticolimbic System and Executive Function. Front. Endocrinol. 2018, 9, 279.
12. Giatti, S.; Garcia-Segura, L.M.; Barreto, G.E.; Melcangi, R.C. Neuroactive steroids, neurosteroidogenesis and sex. Prog. Neurobiol. 2019, 176, 1–17.
13. Janowsky, J.S. The role of androgens in cognition and brain aging in men. Neuroscience 2006, 138, 1015–1020.
14. Resnick, S.M.; Matsumoto, A.M.; Stephens-Shields, A.J.; Ellenberg, S.S.; Gill, T.M.; Shumaker, S.A.; Pleasants, D.D.; Barrett-Connor, E.; Bhasin, S.; Cauley, J.A.; et al. Testosterone Treatment and Cognitive Function in Older Men With Low Testosterone and Age-Associated Memory Impairment. JAMA 2017, 317, 717–727.
15. Nieschlag, E.; Nieschlag, S. Endocrine history: The history of discovery, synthesis and development of testosterone for clinical use. Eur. J. Endocrinol. 2019, 180, R201–R212.
16. Ng, K.; Smith, S.; Shamash, J. Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): Advances and Treatment Strategies in the First-Line Setting. Oncol. Ther. 2020, 8, 209–230.
17. Rice, M.A.; Malhotra, S.V.; Stoyanova, T. Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer. Front. Oncol. 2019, 9, 801.
18. Gim, H.J.; Park, J.; Jung, M.E.; Houk, K.N. Conformational dynamics of androgen receptors bound to agonists and antagonists. Sci. Rep. 2021, 11, 15887.
19. Rehman, Y.; Rosenberg, J.E. Abiraterone acetate: Oral androgen biosynthesis inhibitor for treatment of castration-resistant prostate cancer. Drug Des. Devel. Ther. 2012, 6, 13–18.
20. Guo, C.; Yeh, S.; Niu, Y.; Li, G.; Zheng, J.; Li, L.; Chang, C. Targeting androgen receptor versus targeting androgens to suppress castration resistant prostate cancer. Cancer Lett. 2017, 397, 133–143.
21. Desai, K.; McManus, J.M.; Sharifi, N. Hormonal Therapy for Prostate Cancer. Endocr. Rev. 2021, 42, 354–373.
22. Mitsiades, N.; Kaochar, S. Androgen receptor signaling inhibitors: Post-chemotherapy, pre-chemotherapy and now in castration-sensitive prostate cancer. Endocr. Relat. Cancer 2021, 28, T19–T38.
23. Corona, G.; Filippi, S.; Comelio, P.; Bianchi, N.; Frizza, F.; Dicuio, M.; Rastrelli, G.; Concetti, S.; Sforza, A.; Vignozzi, L.; et al. Sexual function in men undergoing androgen deprivation therapy. Int. J. Impot. Res. 2021, 33, 439–447.
24. Russell, N.; Hoermann, R.; Cheung, A.S.; Zajac, J.D.; Grossmann, M. Effects of oestradiol treatment on hot flushes in men undergoing androgen deprivation therapy for prostate cancer: A randomised placebo-controlled trial. Eur. J. Endocrinol. 2022, 187, 617–627.
25. Bargiota, A.; Oeconomou, A.; Zachos, I.; Samarinas, M.L.; Pisters, L.; Tzortzis, V. Adverse effects of androgen deprivation therapy in patients with prostate cancer: Focus on muscle and bone health. J. BUON 2020, 25, 1286–1294.
26. O'Farrell, S.; Garmo, H.; Holmberg, L.; Adolfsson, J.; Stattin, P.; Van Hemelrijck, M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J. Clin. Oncol. 2015, 33, 1243–1251.
27. Kaplan, M.; Mahon, S.M.; Lubejko, B.G.; Ginex, P.K. Hot Flashes: Clinical Summary of the ONS Guidelines™ for Cancer Treatment-Related Hot Flashes in Women With Breast Cancer and Men With Prostate Cancer. Clin. J. Oncol. Nurs. 2020, 24, 430–433.
28. Khan, A.; Lewis, R.; Hughes, S. Managing Hot Flushes in Men Receiving Androgen Deprivation Therapy for Prostate Cancer. Trends Urol. Men's Health 2014, 5, 31–33.
29. Wibowo, E.; Schellhammer, P.; Wassersug, R.J. Role of estrogen in normal male function: Clinical implications for patients with prostate cancer on androgen deprivation therapy. J. Urol. 2011, 185, 17–23.
30. Beer, T.M.; Schellhammer, P.F.; Corman, J.M.; Glodé, L.M.; Hall, S.J.; Whitmore, J.B.; Frohlich, M.W.; Penson, D.F. Quality of life after sipuleucel-T therapy: Results from a randomized, double-blind study in patients with androgen-dependent prostate cancer. Urology 2013, 82, 410–415.
31. Kaplan, I.; Bubley, G.J.; Bhatt, R.S.; Taplin, M.E.; Dowling, S.; Mahoney, K.; Werner, E.; Nguyen, P. Enzalutamide With Radiation Therapy for Intermediate-Risk Prostate Cancer: A Phase 2 Study. Int. J. Radiat. Oncol. Biol. Phys. 2021, 110,

1416–1422.

32. Hussain, A.; Jiang, S.; Varghese, D.; Appukkuttan, S.; Kebede, N.; Gnanasakthy, K.; Macahilig, C.; Waldeck, R.; Corman, S. Real-world burden of adverse events for apalutamide- or enzalutamide-treated non-metastatic castration-resistant prostate cancer patients in the United States. BMC Cancer 2022, 22, 304.
33. Allan, C.A.; Collins, V.R.; Frydenberg, M.; McLachlan, R.I.; Matthiesson, K.L. Androgen deprivation therapy complications. Endocr. Relat. Cancer 2014, 21, T119–T129.
34. Fisher, W.I.; Johnson, A.K.; Elkins, G.R.; Otte, J.L.; Burns, D.S.; Yu, M.; Carpenter, J.S. Risk factors, pathophysiology, and treatment of hot flashes in cancer. CA Cancer J. Clin. 2013, 63, 167–192.
35. Russell, N.; Hoermann, R.; Cheung, A.S.; Zajac, J.d.; Handelsman, D.J.; Grossman, M. Short-term effects of transdermal estradiol in men undergoing androgen deprivation therapy for prostate cancer: A randomized placebo-controlled trial. Eur. J. Endocrinol. 2018, 178, 565–576.
36. Kouriefs, C.; Georgiou, M.; Ravi, R. Hot flushes and prostate cancer: Pathogenesis and treatment. BJU Int. 2002, 89, 379–383.
37. Qan'ir, Y.; DeDeaux, D.; Godley, P.A.; Mayer, D.K.; Song, L. Management of Androgen Deprivation Therapy-Associated Hot Flashes in Men With Prostate Cancer. Oncol. Nurs. Forum. 2019, 46, E107–E118.
38. Crabb, S.; Morgan, A.; Hunter, M.S.; Stefanopoulou, E.; Griffiths, G.; Richardson, A.; Fenlon, D.; Fleure, L.; Raftery, J.; Boxall, C.; et al. A multicentre randomised controlled trial of a guided self-help cognitive behavioural therapy to MANage the impact of hot flushes and night sweats in patients with prostate CANcer undergoing androgen deprivation therapy (MANCAN2). Trials 2023, 24, 450.
39. Gryzinski, G.M.; Fustok, J.; Raheem, O.M.; Bernie, H.L. Sexual Function in Men Undergoing Androgen Deprivation Therapy. Androg. Clin. Res. Ther. 2022, 3, 149–158.
40. Corona, G.; Rastrelli, G.; Morgentaler, A.; Sforza, A.; Mannucci, E.; Maggi, M. Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores. Eur. Urol. 2017, 72, 1000–1011.
41. Lewis, R.W.; Mills, T.M. Effect of androgens on penile tissue. Endocrine 2004, 23, 101–105.
42. Rizk, P.J.; Kohn, T.P.; Pastuszak, A.W.; Khera, M. Testosterone therapy improves erectile function and libido in hypogonadal men. Curr. Opin. Urol. 2017, 27, 511–515.
43. Hotta, Y.; Kataoka, T.; Kimura, K. Testosterone Deficiency and Endothelial Dysfunction: Nitric Oxide, Asymmetric Dimethylarginine, and Endothelial Progenitor Cells. Sex. Med. Rev. 2019, 7, 661–668.
44. Cunningham, G.R.; Stephens-Shields, A.J.; Rosen, R.C.; Wang, C.; Bhasin, S.; Matsumoto, A.M.; Parsons, J.K.; Gill, T.M.; Molitch, M.E.; Farrar, J.T.; et al. Testosterone Treatment and Sexual Function in Older Men With Low Testosterone Levels. J. Clin. Endocrinol. Metab. 2016, 10, 3096–3104.
45. Wassersug, R.J. Maintaining intimacy for prostate cancer patients on androgen deprivation therapy. Curr. Opin. Support. Palliat. Care. 2016, 10, 55–65.
46. Vitolins, M.Z.; Griffin, L.; Tomlinson, W.V.; Vuky, J.; Adams, P.T.; Moose, D.; Frizzell, B.; Lesser, G.J.; Naughton, M.; Radford, J.E.; et al. Randomized trial to assess the impact of venlafaxine and soy protein on hot flashes and quality of life in men with prostate cancer. J. Clin. Oncol. 2013, 31, 4092–4098.
47. Kim, D.K.; Lee, H.S.; Park, J.Y.; Kim, J.W.; Ahn, H.K.; Ha, J.S.; Cho, K.S. Androgen-Deprivation Therapy and the Risk of Newly Developed Fractures in Patients With Prostate Cancer: A Nationwide Cohort Study in Korea. Sci. Rep. 2021, 11, 10057.
48. Lin, J.K.; Parikh, R.B. Bone Health in Prostate Cancer Survivors: Recent Lessons and Opportunities for Improvement. Eur. Urol. Focus. 2023, 9, 422–424.
49. Chin, K.Y.; Ima-Nirwana, S. The effects of orchidectomy and supraphysiological testosterone administration on trabecular bone structure and gene expression in rats. Aging Male 2015, 18, 60–66.
50. Mohamad, N.V.; Soelaiman, I.N.; Chin, K.Y. A concise review of testosterone and bone health. Clin. Interv. Aging 2016, 11, 1317–1324.
51. Shigehara, K.; Izumi, K.; Kadono, Y.; Mizokami, A. Testosterone and Bone Health in Men: A Narrative Review. J. Clin. Med. 2021, 10, 530.
52. Hussain, A.; Tripathi, A.; Pieczonka, C.; Cope, D.; McNatty, A.; Logothetis, C.; Guise, T. Bone health effects of androgen-deprivation therapy and androgen receptor inhibitors in patients with nonmetastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2021, 24, 290–300.
53. Zhu, X.; Wu, S. Increased Risk of Hypertension with Enzalutamide in Prostate Cancer: A Meta-Analysis. Cancer Investig. 2019, 37, 478–488.

54. Gheorghe, G.S.; Hodorogea, A.S.; Ciobanu, A.; Nanea, I.T.; Gheorghe, A.C.D. Androgen Deprivation Therapy, Hypogonadism and Cardiovascular Toxicity in Men with Advanced Prostate Cancer. Curr. Oncol. 2021, 28, 3331–3346.
55. Agarwal, M.; Canan, T.; Glover, G.; Thareja, N.; Akhondi, A.; Rosenberg, J. Cardiovascular effects of androgen deprivation therapy in prostate cancer. Curr. Oncol. Rep. 2019, 21, 91.
56. Mitsuzuka, K.; Arai, Y. Metabolic changes in patients with prostate cancer during androgen deprivation therapy. Int. J. Urol. 2018, 25, 45–53.
57. Ketchandji, M.; Kuo, Y.F.; Shahinian, V.B.; Goodwin, J.S. Cause of death in older men after the diagnosis of prostate cancer. J. Am. Geriatr. Soc. 2009, 57, 24–30.
58. Ng, C.T.; Bonilla, H.M.G.; Bryce, A.H.; Singh, P.; Herrmann, J. Approaches to Prevent and Manage Cardiovascular Disease in Patients Receiving Therapy for Prostate Cancer. Curr. Cardiol. Rep. 2023, 25, 889–899.
59. Challa, A.A.; Calaway, A.C.; Cullen, J.; Garcia, J.; Desai, N.; Weintraub, N.L.; Deswal, A.; Kutty, S.; Vallakati, A.; Addison, D.; et al. Cardiovascular Toxicities of Androgen Deprivation Therapy. Curr. Treat. Options Oncol. 2021, 22, 47.
60. Kakkat, S.; Pramanik, P.; Singh, S.; Singh, A.P.; Sarkar, C.; Chakroborty, D. Cardiovascular Complications in Patients with Prostate Cancer: Potential Molecular Connections. Int. J. Mol. Sci. 2023, 24, 6984.