Balancing Hormone Therapy

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Balancing Hormone Therapy: Mitigating Adverse Effects of Androgen-Deprivation Therapy and Exploring Alternatives in Prostate Cancer Management

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OVERVIEW

Androgen-deprivation therapy (ADT) is well established as the standard of care in metastatic prostate cancer (PCa) management; however, ADT has significant adverse effects (AEs) that must be addressed. This review aims to highlight opportunities to mitigate AEs of ADT and explore alternatives in PCa management. Specifically, we discuss behavioral and pharmacologic strategies for mitigating ADT AEs as well as ADT-sparing approaches for hormone-sensitive and castration-resistant PCa. Equipped with effective mitigation strategies and possible alternatives, clinicians and researchers can optimize health-related quality of life for patients currently receiving ADT for PCa and consider treatments that spare patients from AEs of ADT.

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer worldwide[1] and is estimated to have caused 34,700 deaths in the United States in 2023.[2] Seminal work in 1941 showed that PCa is androgen-dependent.[3] Androgen-deprivation therapy (ADT) has, therefore, become the mainstay of PCa treatment for patients with metastatic disease.[4] ADT also improves oncologic efficacy of prostate radiotherapy among patients with localized disease.[5] Estimates suggest that over 45% of patients with PCa receive ADT.[4] Treatment advances including ADT have led to improvements in PCa management and survival, with trials reporting median survival of over 6 years for patients with de novo metastatic hormone-sensitive prostate cancer (mHSPC).[6]

Despite its oncologic benefits, ADT can also cause a broad range of adverse effects (AEs) as a consequence of testosterone depletion.[7] Testosterone plays a significant role in maintenance of bone and muscle mass, spermatogenesis, erythropoiesis, and erectile and cognitive function.[8] Additionally, testosterone has been found to be a key player in glucose homeostasis and lipid metabolism, with significant interplay between hypogonadism and development of the metabolic syndrome.[9] Thus, testosterone depletion can lead to numerous AEs that can significantly impair health-related quality of life among ADT recipients.

Widespread use of ADT and the prevalence of ADT-related AEs underscore the importance of identifying strategies to optimize PCa survivorship. In this article, we focus on the evidence base for three approaches to mitigate AEs of ADT: (1) behavioral interventions, (2) the use of bone-resorptive agents (BRAs) to avoid/mitigate the complications of ADT-related bone loss, and (3) ADT-sparing approaches as alternative treatments for patients with metastatic PCa.

BEHAVIORAL TREATMENTS TO MITIGATE AEs OF ADT

ADT-Related AEs Affecting Quality of Life

The increasing number of systematic reviews on the AEs of ADT accentuates the prevalence and importance of ADT-related quality of life impacts for PCa survivors.[10–12] Fatigue is consistently among the most common AEs of cancer and its treatment, and one of the most commonly reported AEs of abiraterone and enzalutamide in phase III trials.[13,14] Risk of fatigue was found to be nearly 50% greater among men initiating ADT before chemotherapy versus after chemotherapy.[13] Patients with PCa receiving ADT experience worsening fatigue over the first year after ADT initiation, particularly those with higher initial Gleason scores and more comorbidities.[15] Depression is a common psychiatric concern with ADT, potentially related to reduced testosterone, changes in immunity and systemic inflammation,[16,17] and/or overall negative impacts on quality of life.[18] A 2017 systematic review and meta-analysis of 18 studies including 168,756 individuals demonstrated a 41% increased risk of depression among patients treated with ADTs.[19] Depression risk was not significantly different for those on continuous ADT compared with those receiving ADT intermittently.[19] Sleep disturbance is another AE of ADT[20,21] that can impair functioning and coping and may mediate ADT-related effects on perceived cognitive function in patients with PCa.[18]

PRACTICAL APPLICATIONS

- Behavioral interventions, such as cognitive behavioral therapy (CBT) and physical activity, can help mitigate adverse effects of androgen-deprivation therapy (ADT), including fatigue, depressive symptoms, and sleep disruption. Behavioral strategies play a critical role in patient-centered clinical practice and can help improve health-related quality of life.
- Bone loss from ADT can be mitigated pharmacologically to reduce fracture risk in hormone-sensitive prostate cancer (PCa) and delay/prevent skeletal-related events (SRE) in castration-resistant PCa (CRPC). Evidence-based practice differentiates reduced bone loss (fracture risk) in hormone-sensitive disease and delayed SRE in CRPC.
- Metastasis-directed therapy (MDT) using radiation represents an appealing strategy for oligometastatic recurrence to delay progression-free survival that is supported by phase II trials. Ongoing trials will determine if MDT in combination with standard treatments in de novo oligometastatic disease confers similar benefit.
- Continuous ADT in CRPC remains standard of care with clinical trials evaluating alternative strategies, such as bipolar androgen therapy, transdermal estradiol, and monotherapy with androgen biosynthesis inhibitors.

Compared with patients with no history of cancer, ADT recipients self-report higher rates of clinically significant sleep disturbance and demonstrate greater objective sleep disturbance within the first year after ADT initiation.[19] Worse sleep disturbance was found to be partly attributable to nocturia and hot flash interference after starting ADT.[19] Sexual dysfunction (eg, decreased libido and erectile dysfunction) is both common and distressing among ADT recipients,[14] with comparable levels of concern reported by patients receiving ADT continuously versus intermittently.[20]

Given the prevalence and breadth of ADT-related AEs, interventions are critical to improve quality of life among ADT recipients. Survivorship guidelines from the National Comprehensive Cancer Network (NCCN) include recommendations for behavioral interventions, such as cognitive behavioral therapy (CBT), exercise/physical activity, and lifestyle modifications, for the management of ADT-related symptoms in survivors.[22] This review focuses on two behavioral interventions with substantial evidence-base for addressing ADT-related AEs through active patient engagement and behavior change—CBT and physical activity—acknowledging that this does not represent an exhaustive list of available non-pharmacologic options for addressing AEs (eg, acupuncture for vasomotor symptoms). Behavioral interventions are advantageous in presenting minimal side effects and lower economic burden relative to pharmacologic and other treatment approaches.[23] As shown in Figure 1, behavioral interventions are also advantageous in their capacity to address multiple AEs simultaneously.[24]

Cognitive Behavioral Therapy

CBT is a well-established, evidence-based treatment for multiple symptoms experienced in cancer survivorship, including fatigue, depression, and sleep disturbance.[19,25] CBT teaches solution-focused cognitive strategies (eg, refocusing away from negative thoughts about symptoms toward more realistic, helpful thoughts) and behavioral strategies (eg, behavioral activation and exposure to feared experiences) within a broader biopsychosocial approach.[24] Cancer-specific CBT interventions can include cognitive and behavioral strategies to improve social support, manage stress, improve health behaviors, and manage symptoms for improved overall physical functioning.[24-26] CBT is associated with reduced fatigue, depression, anxiety, and sleep disturbance, and improved functional and physical quality of life among patients with cancer across sociodemographic characteristics, with moderate to large effect sizes for some symptoms.[25] CBT has been tested with interventionists of varying specialty training (eg, psychologists, social workers, and oncology nurses) and across varying modes of delivery (eg, in person and telemedicine) to ensure accessibility of CBT.[25]

A 2023 systematic review examined the efficacy of CBT interventions for addressing mental and sexual health concerns of PCa survivors in 15 CBT studies,[27] three of which focused exclusively on patients receiving ADT. Overall results support CBT efficacy for improving mental health (eg, distress, depression, and anxiety).[27] However, significant improvements were not found across all studies, and specific effects of CBT for patients after ADT are still being tested.[14] Some variability in reported efficacy of CBT for PCa may be partly attributable to variability in treatment type, intervention targets, and primary outcome measures (eg, overall quality of life).[21] Additional large-scale studies with diverse samples of patients receiving ADT are needed to further examine CBT efficacy. A multicenter randomized controlled trial is currently underway to extend findings from a previous CBT efficacy trial for reducing hot flashes and night sweats among ADT recipients[28] to more diverse patients and to test delivery by oncology nurses.[29] Management of hot flashes is particularly important, given the prevalence,[30,31] persistence,[30] related distress,[31] and potential interference of hot flashes with ADT adherence.[26] Prospective examination has shown that younger age, lower body mass index, and specific genetic polymorphisms are associated with hot flash–related interference in ADT,[32] pointing to potential subgroups for targeted intervention delivery.

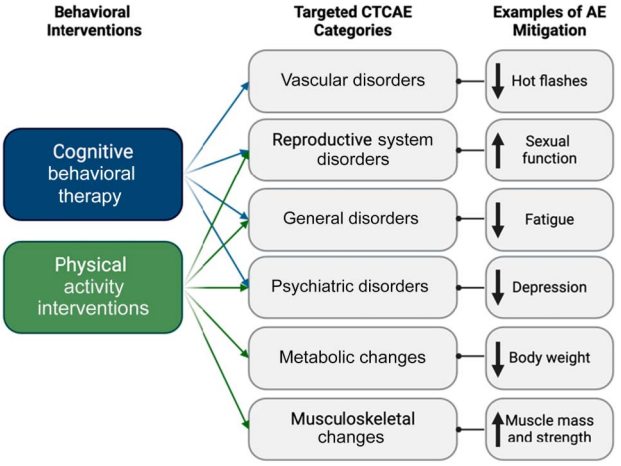

FIG 1. Behavioral interventions to mitigate AEs of ADT. Behavioral interventions, including cognitive behavioral therapy and physical activity interventions, have been shown to help mitigate AEs of ADT across multiple AE categories outlined in the CTCAE. Examples of specific AEs mitigated by behavioral intervention are provided. ADT, androgen deprivation therapy; AEs, adverse effects; CTCAE, Common Terminology Criteria for Adverse Events.

CBT has also shown efficacy for improving sexual health among PCa survivors treated with ADT, including sexual function, desire, and satisfaction.[27] CBT may improve sexual functioning directly by addressing sexual concerns and/or indirectly via improvements in fatigue, mental health challenges, sleep disturbance, pain, body image concerns, and relationship challenges that can subsequently affect sexual functioning.[24] In a 2023 randomized controlled trial among PCa patients with sexual dysfunction, CBT and mindfulness interventions reduced sexual distress and improved sexual satisfaction after intervention, with distress reductions maintained after 6 months.[33] Mindfulness skills are particularly important to Masters and Johnson's (1970) sensate focus foundational approach to sex therapy,[34] which emphasizes touch to minimize sexual performance anxiety. Sensate focus teaches strategies for resolving dysfunctional thinking and optimizing intimacy by encouraging present moment awareness of sensations and discouraging forcing pleasure and arousal.[35] Sensate focus and physical activity are both strongly recommended to help patients maintain sexual satisfaction after ADT.[36]

Broad implementation of evidence-based behavioral interventions like CBT has been hindered by several clinical practice barriers (eg, referral workflows and infrastructure, staffing, and insurance). In 2021, recommendations for addressing many of these challenges were published by the Consensus Panel of the American Psychosocial Oncology Society and the Association of Oncology Social Work. Additionally, an illustrative model for implementing CBT in an interdisciplinary cancer center was published in the Journal of the National Comprehensive Cancer Network in 2023. Ongoing implementation research and clinical practice collaborations are needed to optimize patient access to CBT.

Physical Activity

Physical activity interventions have been shown to be beneficial for improving fatigue, sexual function, and overall quality life[37] as well as markers of metabolic syndrome,[38] cardiorespiratory fitness, incontinence, and muscular strength (eg, preservation of lean mass) among PCa survivors.[39] On the basis of existing evidence in 2014, the American Cancer Society guidelines for PCa were established to broadly recommend engaging in at least 150 minutes of physical activity each week without specifying type of activity.[40] Since then, more physical activity intervention trials have emerged testing physical activity benefits for AEs of ADT. Randomized controlled trial evidence now exists to support the benefits of combined resistance and aerobic exercise programs in the context of ADT without bone metastases to improve muscle mass, strength, physical function, and balance.[41] As recently as 2020, a systematic review of randomized controlled trials for lifestyle interventions to mitigate ADT AEs included 20 physical activity trials, demonstrating the growing focus on physical activity in this specific population.[21] However, methodologic heterogeneity limited conclusions that could be drawn from this review.

A 2018 systematic review of 44 reviews within PCa survivorship more broadly demonstrated the efficacy of physical activity and psychosocial interventions across three domains: (1) health promotion (eg, body weight, body composition, physical activity levels, and prostate-specific antigen [PSA] levels), (2) physical side effects (eg, fatigue, muscle strength, peak oxygen intake, bone health, cardiovascular fitness, sexual function, and incontinence), and (3) psychosocial functioning (eg, quality of life, depression, and anxiety).[39] This review called for more integrated, multicomponent behavioral interventions to address the comprehensive and complex needs of PCa survivorship and requested guideline updates with specific physical activity recommendations inclusive of resistance exercise to protect against treatment-related loss of muscle mass.[39]

PHARMACOLOGIC TREATMENTS TO MITIGATE AEs OF ADT: BRAs

ADT-Related Bone Loss

Skeletal-related morbidity in patients with PCa can be attributed to loss of bone mineral density (BMD) and strength, as well as the direct effect exerted from the pathophysiology of bone metastases. Baseline osteoporosis is observed more frequently among patients with newly diagnosed metastatic disease compared with age-matched controls.[42] ADT can further reduce BMD measured on dual-energy x-ray absorptiometry (DXA) by 8.5% within 6 months of initiation[43] and up to 17% within 2 years.[44]

Loss of serum testosterone can be prolonged even in those patients on shorter duration of adjuvant ADT[45] and causes subsequent loss of circulating estradiol, directly affecting

osteoblast and osteoclast metabolism[46] and leading to significant deterioration in bone microarchitecture.[47] PCa bone metastases exhibit increased osteoblastic activity, masking elevated bone resorption and leading to structural weakening of their surrounding matrix.[48] Almost half of the patients (43%) with bone metastases at presentation, and 5% of M0 patients, will suffer from a skeletal-related event (SRE), namely fractures (fragility or metastatic pathologic fractures), bone pain, hypercalcemia, and/or metastatic spinal cord compression.[49] One fifth of patients with PCa will suffer a fracture within 5 years of initiating ADT.[50]

Bone Protection Agents

Bone protection agents (BPAs) are pharmaceuticals used to reduce BMD loss, including vitamin supplementation and BRAs, namely bisphosphonates and monoclonal antibodies, and selective estrogen receptor modulators (SERMs). Calcium and vitamin D supplementation alone are inadequate for halting the loss of BMD caused by ADT.[51] Bisphosphonates are analogs of pyrophosphate and are commonly grouped into amino-bisphosphonates and non–amino-bisphosphonates. Both cause downregulation of the reticuloendothelial system, downregulating osteoclast activity to inhibit bone resorption.[52] Amino-bisphosphonates (pamidronate, alendronate, risedronate, and zoledronate) are more potent as they inhibit farnesyl pyrophosphate synthase, a key enzyme for osteoclastic activity.[53] Denosumab is a monoclonal antibody that directly inhibits activation of cytokine RANKL, reducing osteoclast production, function, and survival.[54] SERMs (toremifene and raloxifene) maintain BMD in patients with PCa[55]; however, there is concern regarding risk of venous thromboembolism (VTE), with one breast cancer trial demonstrating a 44% increased risk of VTE among patients on long-term raloxifene.[56]

BRAs should be coprescribed with calcium/vitamin D supplementation, and calcium levels should be monitored after initiation. Common AEs are flu-like symptoms, acute-phase reactions, gastrointestinal toxicity, and renal toxicity secondary to acute tubular necrosis.[57] Alopecia and hyperhidrosis are notable common AEs of denosumab alone. Osteonecrosis of the jaw is a rare but serious AE of both bisphosphonates and RANKL inhibitors, necessitating a dental evaluation before initiating such agents.[58] Denosumab has rarely (1.8%) been associated with atypical femoral fractures, particularly in patients with previous bisphosphonate therapy.[59] For patients with hormone-sensitive PCa, denosumab can be given once every 6 months subcutaneously. Although the majority of studies investigate intravenous bisphosphonate use, oral bisphosphonates have been found to have comparative effectiveness at maintaining BMD to treat osteoporosis.[60,61]

Fracture Risk Prediction

Multiple medical societies, including ASCO, the American Urological Association (AUA), the European Association of Urology (EAU), and the European Society of Medical Oncology (ESMO), recommend fracture risk assessment in all patients newly diagnosed with PCa and as part of a holistic follow-up regimen to aid decision making for BRA intervention. The Fracture Risk Assessment Tool (FRAX) is the most widespread method of fracture risk stratification. FRAX uses a 12-point assessment tool to produce an individualized 10-year probability of major osteoporotic and hip fractures. Formal BMD measurement with DXA enhances accuracy; however, a large population study of 28,690 patients with PCa found that only 10% underwent BMD assessment.[62] The UK National Osteoporosis Guideline Group (NOGG) and the US Bone Health and Osteoporosis Foundation[63] have set thresholds for intervention with a BRA based upon risk calculated using FRAX scores, supported by an expert consensus for use in patients with PCa.[64] However, the FRAX score was initially developed for fracture risk assessment in postmenopausal women and, therefore, does not consider several features pertinent to patients with PCa. Despite these limitations, FRAX-predicted fracture risk appears to correlate with observed incidence of fracture among patients with PCa.[65,66]

Appropriate Use and Timing of BPA

Among patients with nonmetastatic PCa receiving ADT, both denosumab and bisphosphonates have been shown to improve or maintain BMD compared with placebo in a network meta-analysis.[67] One trial showed a significant reduction in new vertebral fractures among 764 patients with nonmetastatic HSPC receiving denosumab compared with placebo at 36-month follow-up.[68] By contrast, subanalysis of the nonmetastatic HSPC cohort within the STAMPEDE trial[69] did not demonstrate a statistically significant benefit for the addition of zoledronate in reducing fracture-related hospitalizations.

In patients with mHSPC, subanalysis of the STAMPEDE trial reported that the addition of zoledronate significantly reduced the incidence of fracture-related hospitalisation.[69] The use of denosumab to reduce fracture risk is supported in mHSPC. Zoledronate has been shown to significantly reduce SREs in castration-resistant prostate cancer (CRPC).[70] In metastatic CRPC (mCRPC) with bone metastases, denosumab has demonstrated superior efficacy over zoledronate for time to SRE (20.7 months *v* 17.1; $P = .008$ for superiority) and overall SRE incidence.[71]

The timing, goals, and frequency of BRA differ across PCa populations, and clinicians must be aware of these distinguishing features (Table 1). In general, initiation in metastatic hormone-sensitive disease is intended to reduce the risk of fracture related to osteoporosis, which can be related to ADT but has not been shown in a phase III trial to reduce SREs.[77] In CRPC, BRA is intended to mitigate bone loss caused by ADT and prevent and/or delay SREs, encompassing fracture, need for palliative radiotherapy or surgery, or spinal cord compression. BRA is administered more frequently and with different dosing in this setting.

TABLE 1. Bone-Resorptive Agent Use in Metastatic Hormone-Sensitive and Castration-Resistant Prostate Cancer

Disease Stage	Metastatic Hormone-Sensitive Prostate Cancer	mCRPC With Bone Metastases
Goal of therapy	Reduce fracture risk	SRE prevention/delay
Initiation of therapy	Dependent on fracture risk, commonly using FRAX score	Onset of mCRPC (if not previously received)
Frequency of use	Denosumab 60 mg subcutaneous once every 6 months *or* ZA 5 mg IV annually *or* Oral dosing per manufacturer guidelines (eg, alendronate 70 mg by mouth oncer per week)	Denosumab 120 mg subcutaneous monthly[72] *or* ZA 4 mg once every 12 weeks
Key data to support use	Denosumab *v* placebo: In patients on long-term ADT, one large RCT (n = 1,468) demonstrated denosumab reduced risk of new vertebral fracture at 36 months (1.5% *v* 3.9%; RR, 0.38 [95% CI, 0.19 to 0.78]; *P* = .006). Denosumab significantly improved BMD in the lumbar spine, femoral neck, total hip, and distal third of the radius at 24 months (*P* ≤ .001)[73] ZA *v* placebo: A meta-analysis of 10 placebo-controlled trials of bisphosphonates showed no statistically significant difference in the incidence of fractures compared with placebo (four trials; OR, 1.40 [95% CI, 0.53 to 3.67]; *P* = .50)[74] BMD was improved in the lumbar spine (10 trials; WMD, 6.02 [95% CI, 5.39 to 6.65]; *P* < .001) Secondary analysis of the STAMPEDE trials demonstrated addition of ZA significantly reduced the incidence of FRH in M1 patients (SDHR, 0.73 [95% CI, 0.55 to 0.97]; *P* = .015). However, a higher treatment dosing of ZA was used in this study (4 mg in six 3-weekly cycles, then 4-weekly until 2 years) There is substantial indirect evidence of fracture reduction in other populations with the use of bisphosphonates Oral *v* IV BP: Similar BMD maintenance and fracture incidence with clodronate *v* IV ZA in patients with prostate cancer and bone metastases (3-year fracture incidence was 6% *v* 4% with an overall SRE incidence of 20% *v* 17%; *P* = .62)[73]	Denosumab *v* placebo: A network meta-analysis of two RCTs showed significant reduction in time to first SRE (HR, 0.56 [95% CI, 0.4 to 0.77]; *P* = .002)[75] Bisphosphonates *v* placebo: Network meta-analysis of nine trials demonstrated marginal reduction in SREs (OR, 0.79 [95% CI, 0.62 to 1.00]; *P* = .05)[76] Denosumab *v* ZA: Randomized double-blinded phase 3 trial. Median time to first SRE was delayed by 3.6 months by denosumab compared with ZA (20.7 *v* 17.1 months; *P* = .0002 for noninferiority; *P* = .008 for superiority)[71] Similar rates of SREs with denosumab and zoledronic acid: Spinal cord compression (3% *v* 4%) Need for palliative radiation (19% *v* 21%) Pathologic fracture (14% *v* 15%) Denosumab was associated with greater rates of grade 3 or higher adverse events than ZA (72% *v* 66%; *P* = .01) and unspecified hypocalcemia (13% *v* 6%; *P* < .0001)

Abbreviations: ADT, androgen-deprivation therapy; BMD, bone mineral density; BP, bisphosphonate; FRAX, fracture risk assessment tool; FRH, fracture-related hospitalizations; HR, hazard ratio; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SDHR, subdistribution hazard ratio; SRE, skeletal-related event; WMD, weighted mean difference; ZA, zoledronic acid.

ASCO guidance (2020) recommends use of denosumab preferentially or bisphosphonates as an alternative in patients with nonmetastatic PCa receiving ADT who are at high risk of fractures using FRAX and in all patients with mCRPC.[78] EAU and NCCN guidelines both recommend BRA use in patients with CRPC with bone metastases, given the higher incidence of SREs in this population relative to hormone-sensitive disease. Notably, a risk-stratified approach is recommended in patients on long-term ADT without bone metastases, with BRA use in patients with one additional clinical risk factor, a severe fracture on treatment, and/or with annual BMD loss confirmed to be >5%.[79] ESMO recommends BRA use in mCRPC and patients with symptomatic bone metastases. ESMO also uses a risk-stratified approach

for ADT recipients, with BRA recommended if two clinical risk factors are present.[80]

There is a paucity of evidence for the timing and duration of BRAs in hormone-sensitive disease. Given that ADT affects bone quality within 6 months of initiation,[43] coprescription at ADT initiation should be considered in those at higher risk for fracture. For patients with localized disease, duration of BRA will depend on the duration of androgen deprivation and their individualized risk once ADT has ceased. Patients on lifelong ADT should be re-evaluated for fracture risk at the time of any change in therapies (eg, initiation of a corticosteroid or new therapies) and/or the development of an SRE. The NCCN recommends DEXA imaging every 1-2 years for those on ADT.[81] Fracture incidence does not appear to differ for intermittent versus continuous ADT.[82] However, BPA is more likely to continue lifelong or until treatment risks outweigh potential benefits among patients with metastatic disease.

Importantly, fracture risk is closely associated with fall risk, and PCa itself may result in loss of muscle mass and proprioception.[83] Thus, a holistic approach, inclusive of lifestyle interventions (eg, physical activity and nutrition) and BPA, is critical to overall PCa management.

ALTERNATIVES TO ADT STANDARD CARE REGIMENS FOR METASTATIC PROSTATE CANCER

Metachronous or Oligometastatic Recurrent HSPC

Stereotactic Ablative Body Radiotherapy

The SABR-COMET trial was the first randomized phase II trial to show progression-free survival (PFS) and overall survival benefit for stereotactic ablative body radiotherapy (SABR) versus standard of care in oligometastatic prostate, breast, and lung cancers.[84] Two dedicated randomized trials in oligorecurrent or metachronous hormone-sensitive prostate cancer (HSPC; ORIOLE and STOMP) randomly assigned patients to SABR or observation. In the ORIOLE phase II trial, 54 patients with 1-3 metastases visible on conventional imaging were randomly assigned 2:1 to SABR versus observation. The primary outcome was 6-month PFS, where progression was defined as a PSA rise of at least 2 ng/mL and 25% above nadir, progression on conventional imaging, ADT initiation, or death. All SABR patients underwent a piflufolastat F-18 prostate-specific membrane antigen (PSMA) positron-emitting tomography (PET) scan at baseline and day 180. Progression was found in 11/18 (61% [95% CI, 38.5 to 79.6]) of patients in the observation arm and 7 of 36 (19% [95% CI, 9.6 to 35.4]) in the SABR arm ($P = .005$).[85] Importantly, 16 of 36 patients had baseline PSMA PET–avid lesions that were not included in the radiation treatment fields because the metastases to radiate were determined on the basis of conventional imaging. Six of the 16 (38% [95% CI, 18.5 to 61.5]) had progression at 6 months, highlighting the importance of using the most sensitive imaging available to target lesions.[85]

The STOMP (Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence) phase II trial used 18-F choline PET for determination of metastatic sites. Ost et al[86] reported a median ADT-free survival of 21 months (80% CI, 14 to 29) with SABR versus 13 months (80% CI, 12 to 17) with observation (hazard ratio [HR], 0.60 [80% CI, 0.4 to 0.9]; $P = .11$)[86]; the criteria for initiating ADT was progression to >3 metastases, local progression of baseline metastases, or symptomatic metastases. In contrast to the ORIOLE trial, a PSA rise alone was not sufficient to initiate ADT in the STOMP trial. Five-year follow-up analyses demonstrated that 34% of the metastasis-directed therapy (MDT) group remain ADT-free at 5 years, in contrast to 8% of those on surveillance (HR, 0.57 [80% CI, 0.38 to 0.84]; $P = .06$).[86]

Retrospective series using the SABR approach with and without concurrent ADT in hormone-sensitive disease highlight differences in clinical practice, given the lack of randomized data to determine the role of ADT in this setting. A multicenter experience of 305 patients with oligorecurrent disease who also underwent PSMA PET–directed MDT evaluated the role of ADT, which was used in 38% of patients. This series found that ADT improved biochemical PFS (HR, 0.28 [95% CI, 0.16 to 0.51]; $P < .0001$), although outcomes did not differ between patients who received ≤6 months of ADT and those who received no ADT.[87] The phase II EXTEND trial used a different design, treating all 87 patients with intermittent ADT and then randomly assigning patients to the SABR component. EXTEND found that SABR delayed time to progression in the SABR + ADT arm (median not reached) versus ADT alone (15.8 months [95% CI, 13.6 to 21.2]; HR, 0.25 [95% CI, 0.12 to 0.55]; $P < .001$).[88] The use of concurrent hormones is being studied in several randomized trials of stereotactic body radiotherapy (SBRT) alone versus in combination with fixed courses of ADT and an androgen receptor signaling inhibitor (ARSI; eg, DART [NCT04641078], RADIOSA [NCT03940235], SPARKLE [NCT05352178], and ADOPT [NCT04302454]).

Radiopharmaceuticals ± MDT

Evaluating radiopharmaceuticals with or without MDT represents another strategy under investigation in HSPC that is ADT-sparing. In a pilot study of 10 patients with HSPC and <10 metastases on PSMA PET, patients received two cycles of lutetium-177-PSMA-617 (lutetium Lu 177 vipivotide tetraxetan) without ADT. With a median follow-up of 28 months (range, 11-39 months), the median PFS was 11 months (range, 4-39 months), and the median ADT-free survival was 16 months (7-39 months). Five of the 10 patients achieved a 50% decline in PSA, which was predictive of a longer ADT-free survival.[89] This pilot study supports the ongoing LUNAR study (ClinicalTrials.gov identifier: NCT05496959) that will randomly assign 100 patients with

oligorecurrent (1-5 sites) metastatic PCa to receive lutetium-177-PSMA-617 plus SABR versus SABR alone using a dose-adapted SBRT approach in the lutetium-177-PSMA-617 arm. The primary end point is PFS, with secondary end points including ADT-free survival.[90] The RAVENS (ClinicalTrials.gov identifier: NCT04037358) trial will evaluate SBRT alone versus in combination with radium-223. The BULLSEYE (ClinicalTrials.gov identifier: NCT04443062) trial will compare standard of care versus lutetium-177-PSMA-617 (without ADT).

Transdermal Estradiol Patches

Long before the contemporary ongoing trials focused on SBRT, during 2008-2017, the phase II/III PATCH (Prostate Adenocarcinoma Transcutaneous Hormone) trial randomly assigned patients with locally advanced and metastatic HSPC to luteinizing hormone release hormone (LHRH) agonists versus transdermal estradiol patches (tE2). Exogenous estrogen leads to a negative feedback loop on the hypothalamus and pituitary that can achieve castrate levels of testosterone while minimizing the estrogen-depleting effects on bone health, as well as avoidance of hot flashes. tE2 in contrast to oral exogenous estrogen bypasses first pass hepatic metabolism, offering decreased thromboembolic risk and a potential decrease in cardiovascular toxicity; the primary end point of the PATCH trial was to evaluate cardiovascular mortality or morbidity between the two cohorts, which ultimately did not show a difference.[91] However, this study did report that global QOL scores were higher in the tE2 cohort relative to LHRH agonists (mean difference, 4.2 [95% CI, 1.2 to 7.1]; $P = .006$).[91,92] This strategy is not recommended for clinical practice as it failed to meet the primary endpoint, but highlights ongoing efforts for LHRH agonist alternatives with a trial design that captured patient reported outcomes.

De Novo Metastatic HSPC

Patients with de novo or synchronous metastatic disease may have a different disease biology than patients who develop oligometastatic recurrence.[93,94] In de novo metastatic disease, the approach under evaluation is intended to limit ADT duration, rather than completely avoid ADT.

MDT and Fixed Courses of Hormones

Importantly, there are no randomized trial results to support abbreviated courses of ADT with MDT and multimodality therapy in de novo metastatic disease. Enthusiasm for this approach stems from relatively small open-label trials and retrospective series. In one series of 52 patients with de novo oligometastatic HSPC, patients received ADT with docetaxel (abiraterone with prednisone was also allowed), prostatectomy, adjuvant radiation, and MDT. Eighty percent of patients achieved an undetectable PSA with testosterone recovery.[95] Another series of 20 patients with de novo metastatic PCa treated patients with ADT, prostatectomy, and MDT; in this study, four (20%) patients achieved an undetectable PSA with recovered testosterone.[96] The duration of hormonal therapy has also varied across series. Despite the lack of randomized trial data for the use of MDT in this patient population, a recent report from the Advanced Prostate Cancer Consensus Conference (APCCC) on the management of patients with metastatic PCa found that 61% of panelists (international PCa experts) voted for systemic therapy plus local treatment to the primary tumor and MDT in patients who presented with de novo oligometastatic disease, while 33% voted for systemic plus local treatment to just the primary.[97] Fortunately, there are multiple ongoing trials for patients with metastases at diagnosis which use a backbone of ADT, ARSI, and prostate-directed radiation as SOC plus randomized SBRT for the metastasis component (PLATON: NCT03784755, TERPS: NCT05223803; START MET: NCT05209243). These trials require oligometastatic disease, given that the SBRT component must be limited. Results will be truly informative for evidence-based practice.

In contrast to trials requiring oligometastatic disease, there are fewer trials for patients with de novo metastatic disease of higher volume that adopt an ADT-limiting or fixed course of ADT. The Alliance ADREAM trial (ClinicalTrials.gov identifier: NCT05241860) is evaluating the cessation of ADT and ARSI in patients with exceptional responses (defined as PSA <0.2 ng/mL) at 24-36 months to assess the durability of response in the ADT-free period; the primary end point is to determine the proportion of patients who experience an 18-month treatment-free interval from therapy with eugonadal testosterone (to ≥150 ng/mL) after treatment interruption. Patients are allowed, but not required, to have had SBRT to metastases before enrollment, and either de novo or metachronous disease is allowed. Although there may be an inherent bias to enroll the patients with oligometastatic disease, the burden of disease will be collected on trial and offer insights into determining patients suitable for this approach.

Intermittent ADT Alone

Given the robust data for doublet and triplet therapy, intermittent ADT is generally not favored for metastatic HSPC. However, this strategy remains appropriate for select patients appropriately counseled on the alternatives. SWOG9346 evaluated intermittent versus continuous ADT in an era long before doublet (ADT + ARSI or docetaxel) or triplet therapy (ADT + docetaxel + ARSI). This trial, however, was statistically inconclusive for noninferiority as the confidence interval for the HR for death exceeded the upper boundary of noninferiority. For this reason, continuous ADT has been the backbone of treatment in clinical and research practice.

Metastatic Castration-Resistant Prostate Cancer

Standard practice upon the development of CRPC is continuation of ADT, as endorsed by NCCN, AUA, and EAU guidelines. The rationale is that surviving hormone-sensitive clones require ongoing suppression. Even in

CRPC, androgens and androgen receptor ligands continue to play a role, and androgens that are not suppressed may reinvigorate growth of cancer.[98]

In 1993, Taylor et al published a retrospective analysis of 341 patients treated across four trials in CRPC conducted during an era where ADT was not mandated as part of eligibility. This allowed for comparisons between patients who did and did not receive ADT, albeit the use of ADT was determined by physician/patient decision, not randomized.[99] The trials included those evaluating doxorubicin, carboplatin, and ketoconazole. In this series, 287 of 341 patients (84%) continued ADT or had undergone an orchiectomy, and 54 patients (16%) had discontinued exogenous hormones. When controlling for other prognostic factors, a survival benefit of 2-6 months was identified.[99] Taylor et al (1993) summarized individual trials rather than conducting a meta-analysis, and did not report testosterone levels at trial entry nor on study. All current FDA approvals in CRPC are with agents that were studied in combination with ADT in their respective randomized trials.

Bipolar Androgen Therapy

Perhaps the most well-studied approach challenging the dogma of ongoing castration in CRPC is bipolar androgen therapy (BAT). BAT involves rapid cycling between high and low testosterone. Preclinical studies documented that episodic exposure to supraphysiologic testosterone could down-regulate androgen receptor (AR) levels that could resensitize cells to androgen ablation.[100] The TRANSFORMER open-label phase II study involved patients who were asymptomatic but progressing on abiraterone acetate with prednisone (AAP). These patients were randomly assigned to BAT versus enzalutamide, with crossover allowed upon progression. Patients received monthly intramuscular testosterone or daily oral enzalutamide, with all patients receiving LHRH agonists or antagonists. One hundred ninety-five patients were randomly assigned and included in the intention-to-treat population. The primary end point, PFS, was similar for both arms, 5.6 months in the BAT arm and 5.7 months in the enzalutamide arm (HR, 1.13 [85% CI, 0.83 to 1.57]; $P = .45$), as was overall survival (32.9 versus 29.0 months; HR, 0.95 [95% CI, 0.66 to 1.39]; $P = .80$).[101] Thirty-seven (39.3%) patients on the BAT arm crossed over to enzalutamide on progression and 48 (47.6%) patients on enzalutamide crossed over to BAT. A similar number of patients in each arm did not cross over due to clinical progression (14%-18%). Upon crossover, PFS was longer in those patients who switched from BAT to enzalutamide: 28.2 months compared with enzalutamide to BAT 19.6 months (HR, 0.44 [95% CI, 0.22 to 0.88]; $P = .02$). Patient-reported QOL favored BAT at 1, 3, and 6 months, particularly for fatigue.[101]

ADT + AAP or AAP Alone

In the exploratory phase II SPARE trial, 68 patients with chemotherapy-naïve mCRPC were randomly assigned to AAP with (arm A) or without (arm B) ADT, thus testing the benefit of the LHRH therapy. Testosterone was below castrate levels for all patients at baseline and while on study, and radiographic PFS (rPFS) was similar between arms. Twelve-month rPFS was 84% in arm A and 89% in arm B. Luteinizing hormone (LH) and follicle-stimulating hormone increased in the AAP alone arm within a few cycles as a consequence of discontinuation of LHRH analogs, consistent with hypergonadotropic hypogonadism.[102] Not surprisingly, discontinuation of AAP in the monotherapy arm led to more rapid testosterone recovery in 6 of 34 patients, which could be problematic in a more advanced patient population transitioning to another line of therapy. Overall, SPARE was exploratory in nature as it was not statistically powered for definitive conclusions; SPARE serves as a hypothesis-generating but not practice-changing study. While not ADT sparing, the randomized phase 2 ARTO trial treated all patients with oligometastatic newly CRPC with LHRH analogs and AAP, randomizing one arm to receive SBRT as well; this yielded a significant PFS benefit with the addition of SBRT (HR 0.35, 95% CI, 0.21-0.57; $P < .001$).[103] Taken together with trials in oligorecurrent hormone sensitive disease, this trial highlights the expanding role of SBRT to delay metastases, even in CRPC.

There remains enthusiasm for ADT-sparing or ADT-limiting approaches across the advanced PCa disease spectrum, and participation in clinical trials is fundamental to our understanding of when or for whom these approaches may be appropriate. Ongoing phase III randomized trials should include patient-reported toxicity, and efficacy outcomes that will determine potential new standards of care. Transparent communication about goals of therapy, treatment rationale, and experience to date will be critical to informed patient decision making on ADT-sparing/ADT-limiting approaches.

CONCLUSION

This review identified three evidence-based approaches to address AEs of ADT, namely behavioral and pharmacologic strategies, and ADT-sparing approaches for metastatic PCa. A thorough understanding of available approaches can equip clinicians to appropriately inform patients of ADT-related AEs, effective mitigation strategies, and possible ADT alternatives, and engage patients in shared decision making before, during, and after treatment. Moreover, clinicians can use available approaches to tailor AE interventions to patient needs and preferences, consistent with the aims of patient-centered, personalized medicine. Future research on mediators and moderators of intervention effects across each of these approaches will further our understanding of underlying mechanisms and for whom these intervention strategies work best. Ultimately, effectively managing and/or avoiding ADT-related AEs has the potential for significant public health impact by optimizing health-related quality of life in the growing population of patients receiving ADT for PCa.

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