Androgen deprivation therapy: indications, methods of utilization, side effects and their management

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Our objective is to provide an up-to-date summary of current literature on the indications for androgen deprivation therapy (ADT), ways in which ADT is used, and the main side effects associated with its use.

MEDLINE (Pubmed) was searched for relevant papers published from database inception to May 1, 2019 for studies evaluating the use of ADT and its associated adverse events.

ADT is a mainstay in the treatment of prostate cancer and is used throughout the disease course. While predominantly used in the metastatic setting, ADT has a role in the treatment of localized disease and in the management of recurrent cancer. Intermittent ADT has an application for a certain subset of men with recurrent and metastatic disease who have significant side effects. Associated side effects of ADT are wide ranging and include osteoporosis with an associated increased fracture risk, elevated rates of diabetes, metabolic syndrome, cardiovascular risk, sexual dysfunction and hot flashes. As ADT has a variety of associated side effects, care for men receiving ADT is best managed in a multidisciplinary setting with active participation between the treating physician (urologist, radiation oncologist) and their primary care physician.

Key Words: androgen deprivation therapy, indications, management

Introduction

Androgen deprivation therapy (ADT) plays a significant role in the treatment of men with localized, recurrent and metastatic prostate cancer. Almost half of all men treated for prostate cancer receive ADT at some point in their treatment pathway.[1,2] As ADT can cause significant adverse sequalae and negatively impact patient's quality of life it is important for both the treating urologist and family physician to have a comprehensive understanding of anticipated side effects and how best to manage them. This review will summarize the indications for ADT, methods of utilization, and ADT's associated adverse events.

Indications for ADT

Prostate cancer, until the latter stages of the disease, is a hormone sensitive disease. Huggins and Hodges first illustrated the androgen dependency of prostate cancer in 1941 by demonstrating that the androgen blockage achieved through orchiectomy was an effective treatment for symptomatic, metastatic prostate cancer.[3] Since that point in time however, luteinizing hormone-releasing hormone (LHRH) agonists and antagonists have been developed which allow for the medical suppression of testosterone; these agents allow for the reversibility of therapy and avoid the negative physical and psychological effects of orchiectomy.[4-6]

ADT (both LHRH agonists and antagonists), due to prostate cancer's androgen susceptibility, is a mainstay of treatment and can be used at different points in the prostate cancer treatment pathway. In patients with localized disease pursuing curative intent strategies (i.e.: surgery or radiation) ADT has been shown to improve survival when used in conjunction with radiation therapy for patients with intermediate and high-risk disease.[7] Patients with intermediate risk disease are typically given a short course of ADT (4-6 months), while those with high-risk disease are treated for 2-3 years with continuous ADT to help reduce the risk of recurrence through treatment of occult systemic

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disease.[8] In patients with non-metastatic, recurrent prostate cancer or localized prostate cancer who are not suitable for curative therapy, ADT should only be used in patients requiring symptom control, when PSA > 50 mg/mL or PSA doubling time < 12 months.[9,10]

The majority of ADT however, is used in the metastatic prostate cancer setting. Patients with metastatic, symptomatic disease require immediate initiation of treatment.[4] However, there are no clear cut offs regarding when to start ADT for those who have documented metastatic disease but remain asymptomatic.[4] A Cochrane review which included four randomized controlled trials (all of which were completed in the pre-PSA era) evaluating immediate versus deferred ADT demonstrated that there was no difference in prostate cancer specific survival between groups although immediate ADT reduced disease progression.[11] The lack of conclusive guidelines is in part due to poorly conducted trials and heterogeneity in study populations which have prevented reliable conclusions to be drawn from their analyses.

Along the disease trajectory, due to long term androgen deprivation, prostate cancer transforms from a hormone sensitive state, in which testosterone blockade is effective at controlling disease, to one that is castrate resistant. At this point, despite low levels of testosterone (testosterone < 50 ng/dL or 1.7 nmol/L), the disease begins to progress. In these cases, additional medications such as docetaxel (chemotherapy), enzalutamide/abiraterone/apalutamide/darolutamide (advanced antiandrogens), radium-223 (bone targeted therapy) are added to the baseline ADT.[4]

Utilization of ADT

Continuous versus intermittent ADT

In the setting of metastatic hormone sensitive prostate cancer, ADT can be administered in either a continuous or intermittent fashion. Initial interest in intermittent ADT was driven by a theory that intermittent androgen deprivation could prolong the time to castrate resistance and thereby lengthen survival.[12] In the largest randomized controlled trial evaluating intermittent versus continuous ADT, the results were inconclusive.[13] As a non-inferiority trial, Hussain et al were unable to rule out a 20% increased risk of death with intermittent therapy compared to continuous. Moreover, of the 3040 patients recruited, only 1535 were eligible for inclusion, illustrating that at best only 50% of patients are candidates for intermittent therapy. A meta-analysis including data from 6856 patients demonstrated no significant difference between intermittent and continuous therapy for overall survival (HR: 1.02; 95%CI: 0.93-1.11), cancer specific survival (HR: 1.02; 95%CI: 0.87-1.19) or progression free survival (HR: 0.94; 95%CI: 0.84-1.05).[14] Patients, did however, report a modest improvement in mental health and sexual function over the short term with intermittent therapy. To better elucidate the durability of benefits seen, Hershman et al reported on long term data from a cohort of patients randomized to intermittent and continuous ADT. Using 10-year incidence rates they found that there was no reduction in bone or endocrine related events but increased incidence of ischemic and thrombotic events.[15] Given the lack of benefit from a survival perspective and conflicting data with respect to adverse events intermittent therapy should be reserved for well-informed patients who have considerable side effects secondary to ADT.

Side effects of ADT and their management:

Bone health

ADT is associated with a decrease in bone mineral density (BMD) as well as an increased risk of fracture. Several prospective studies have shown that BMD decreases by 5%-10% in the first year after starting ADT.[16-19] In retrospective studies using large administrative datasets, ADT use resulted in a small, but statistically significant increase in fracture rates.[20] Smith et al, reported that patients on ADT were at 1.14 times the risk of fracture than those unexposed to ADT after controlling for age, race and incident bone metastases.[21] In a more recent propensity matched retrospective study, patients on ADT were found to have 1.39 times the risk of fractures compared to their unexposed controls.[2] Moreover, the fracture risk increases with longer duration of ADT use.[20]

As a result of the risk of declining BMD secondary to ADT use, existing literature recommends screening for baseline BMD at the time of ADT initiation to allow for risk stratification.[4] A retrospective study from the Veterans Administration demonstrates that only 20% of patients initiated on ADT undergo BMD screening.[22] In a large retrospective study using a administrative database, the involvement of a primary care provider greatly increased the likelihood of BMD testing compared to when a urologist alone cared for the patient.[23] Recognition and management of decreased BMD is important in this patient population since the development of a fracture is associated with decreased overall survival.[24]

Patients on ADT are routinely recommended to supplement their diet with calcium and vitamin D. However, there are no randomized trials that have

demonstrated whether supplementation improves BMD in this population. Currently the National Osteoporosis Foundation recommendations a daily calcium intake of at least 1200 mg (from diet and supplements) and daily vitamin D supplement of 800-1000 IU for all men over the age of 50.[25] These recommendations would seem appropriate for men receiving ADT as well.

Various agents are available to help manage the deleterious bone health effects of ADT. Randomized trials have demonstrated that bisphosphonates are effective at increasing BMD or reducing the loss of BMD in patients on ADT. In a 2001 study evaluating pamidronate 60 mg every 12 weeks, there was a 3.3% decrease in BMD in the lumbar spine, 2.1% in the trochanter and 1.8% in the hip in patients randomized to ADT alone versus those receiving ADT plus pamidronate.[26] In a study evaluating risedronate versus placebo, patients in the placebo arm were found to have decreased BMD versus stable BMD in the risedronate group.[27] A meta-analysis including data from 2634 patients showed treatment with bisphosphonates resulted in increased BMD, whereas patients treated with placebo had decreased BMD.[28] Moreover, the use of bisphosphonates were shown to reduce the risk of fractures (RR: 0.80, $p = 0.005$) and a formal diagnosis of osteoporosis (RR: 0.39, $p < 0.001$).[28]

Denosumab is a human monoclonal antibody directed against RANK-L (receptor activator of nuclear factor kB ligand), which is a key mediator of osteoclast formation, function and survival. A 2009 randomized study found that denosumab increased BMD in the lumbar spine at 2 years by 5.6% compared with a 1% loss in the placebo group ($p < 0.001$).[29] Similar improvements in BMD were seen in the hip, femoral head and radius. Moreover, denosumab use led to decreased vertebral fractures at 3 years (1.5% versus 3.9%; RR: 0.38; 95%CI: 0.19-0.78; $p = 0.006$).

As men who receive ADT experience greater BMD loss than normal and are therefore at higher risk for fractures, current National Comprehensive Cancer Network guidelines suggest ensuring adequate intake of calcium and vitamin D and obtaining a baseline BMD test to determine baseline risk for patients on long term ADT.[30] In one study the provision of focused education on bone health was associated with a trend towards improved adherence to vitamin D and calcium intake.[31] Further treatment with bisphosphonates (aldendronate, zoledronic acid) or denosumab is recommended for men with a T score ≤ -2.0 at the lumbar spine, femoral neck or hip or if the 10-year risk of fracture is greater than 20% for any major fracture or greater than 3% for hip fracture.[30]

Metabolic consequences

The use of ADT has known metabolic consequences. This is supported by both prospective and population level evidence. Several small, prospective studies found that the use of ADT was associated with weight gain, increased body fat percentage, greater insulin resistance and elevated fasting glucose levels.[32-34]

The link between ADT use and diabetes risk raised by the smaller, initial studies was later confirmed by several large population-based studies. In one study, the US-based SEER-Medicare database was used, including over 70,000 men over the age of 65 with prostate cancer; they found a 44% increased risk of incident diabetes in the cohort being treated with ADT.[35] Another study using the Veterans Administration database, reported similar findings; in men treated with ADT there was a 28% increased risk of incident diabetes.[36] Finally, using an administrative database from Ontario, Canada over 19,000 men over the age of 66 treated with > 6 months of ADT or bilateral orchiectomy were examined.[37,38] The receipt of ADT or bilateral orchiectomy was associated with an increased risk of diabetes (HR: 1.24; 95%CI: 1.15-1.35).

The diagnosis of metabolic syndrome requires the presence of three of five criteria: 1) serum triglycerides > 150 mg/dL (1.7 mmol/L), 2) high density lipoprotein (HDL) < 40 mg/dL (1.0 mmol/L), 3) fasting serum glucose > 110 mg/dL (6.1 mmol/L), 4) waist circumference > 102 cm, and 5) blood pressure ≥ 130/85.[39] ADT has been shown to increase waist circumference secondary to weight gain and risk of diabetes. Triglycerides have also been shown to be affected by ADT; triglycerides of patients on ADT increased by 26.5% (± 10%; $p = 0.01$) after 1 year of treatment.[32] Metabolic syndrome as a composite outcome was assessed by Braga-Basaria et al, illustrating that metabolic syndrome was present in more than 50% of patients treated with long term ADT. The main drivers of the metabolic syndrome diagnosis were abdominal obesity, hyperglycemia, and elevated triglycerides.[40]

The impact of exercise in the setting of ADT has been evaluated. Galvao et al conducted a randomized, multicentre trial evaluating supervised exercise versus physical activity with printed material in men previously treated with ADT. Improvements were seen in cardiovascular fitness, muscle strength, and self-reported physical functioning.[41] However, no significant differences were found between groups with respect to total body weight or waist circumference. The patients receiving supervised exercise sessions had increased HDL levels at 1 year (0.13 mmol/L; $p = 0.001$). As a result of this and other smaller studies which showed mixed results,[42,43] it is not entirely clear what degree

of benefit is derived from exercise in the prevention or treatment of metabolic syndrome. However, the recommendation for routine physical activity is sensible.

Due to the increased risk of insulin resistance and incident diabetes while receiving ADT, these men could be considered high risk and thus screened as such.[44] Regular blood glucose monitoring of patients with pre-existing diabetes to ensure adequate control is maintained would also be prudent. Triglyceride abnormalities should be treated as per guidelines to minimize cardiovascular risk.

Cardiovascular disease

The link between ADT and cardiovascular disease has evolved over the past two decades. The first study to evaluate the association was a SEER-Medicare study which evaluated over 70,000 men with prostate cancer.[35] Keating et al found that men receiving LHRH agonists had a 16% increased risk of coronary heart disease, an 11% increased risk of myocardial infarction (MI) and a 16% increased risk of sudden cardiac death compared to prostate cancer patients not on ADT. The association between ADT and increased cardiovascular risk was reproduced in a later study which showed that patients with newly diagnosed prostate cancer receiving LHRH agonists experienced a 20% increase in cardiovascular mortality over a 5 year follow up period.[45] These publications led to a FDA imposed modification of ADT drug labels to include the risk of cardiovascular outcomes secondary to therapy.[46]

However, not all studies reproduced evidence of this association. Alibhai et al retrospectively evaluated records for approximately 20,000 men in Ontario and did not find evidence of an association between ADT and acute MI (HR: 0.91; 95%CI: 0.84-1.00) or sudden cardiac death (HR: 0.96; 95%CI: 0.83-1.10).[37] Furthermore, four post-hoc analyses of randomized controlled trials reported no association between ADT and cardiovascular mortality.[47-50] These findings were supported by a meta-analysis of eight randomized controlled trials which found that there was no difference in risk of CV death in patients receiving ADT versus those who did not (RR: 0.93; 95%CI: 0.79-1.10; p = 0.41).[51]

The relationship between ADT and cardiovascular events has also been examined accounting for a patient's baseline cardiovascular risk. Two retrospective studies found that ADT use was associated with increased risk of all-cause mortality only among patients with a previous myocardial infarction or diagnosis of congestive heart failure.[52,53] However, this link is not definitive as a large SEER-Medicare study found that baseline comorbidity did not modify impact of ADT on the risk of MI[54] and re-analysis of two randomized trials stratifying by morbidity did not find that men with pre-existing cardiovascular disease had excess cardiovascular deaths.[48,49]

The difficulty in interpreting these conflicting studies stems from the heterogeneity of patient populations, outcome definitions and study design. The only studies to show a relationship between ADT and increased cardiovascular risk feature observational designs whereas, no re-analysis of randomized trial data has yielded evidence of an association. However, no clinical trial was specifically designed to evaluate cardiovascular risk and therefore the limitations inherent to post hoc analyses must be appreciated. The mechanism for association between ADT and cardiovascular disease may be linked to metabolic effects which have been more conclusively delineated. Therefore, management of metabolic syndrome may help to mitigate increased cardiovascular risk if there is a true association.[44]

In the above-mentioned trials, the majority of patients were receiving LHRH agonists and therefore studies have sought to determine if LHRH antagonists may have a different risk profile. A pooled analysis including six randomized trials of degarelix (LHRH antagonist) versus leuprolide (LHRH agonist) found that degarelix was associated with a lower risk of cardiovascular events (HR: 0.60; 95%CI: 0.38-0.94; p = 0.025); degarelix was found to be even more protective in patients with baseline cardiovascular disease compared to leuprolide (HR: 0.476; 95%CI: 0.260-0.871; p = 0.016) (55). Care should be taken when interpreting these results since it was a post hoc analysis, but it suggests that for patients with baseline cardiovascular disease, LHRH antagonists may be the preferred method of testosterone suppression.

Sexual dysfunction:

Sexual dysfunction affects over 90% of men receiving ADT.[56] For patients who have already received primary therapy, sexual function may already be significantly affected, and the addition of ADT further exacerbates pre-existing problems. ADT, because its very nature of sharply reducing testosterone levels, is associated with a decrease in sexual desire and erectile function.[44] Limited options are available to mitigate the sexual side effects of ADT. Intermittent ADT, by allowing for testosterone recovery in between treatment cycles, may allow a select group of patients reprieve from the sexual side effects. Crook et al demonstrated that men on intermittent therapy had greater desire for sexual activity compared to men on continuous therapy[57] and Hussain et al demonstrated that erectile function

was significantly better in the intermittent group.[13] However, intermittent therapy is not suitable for all patients and the trade off between adverse sexual side effects and oncological control needs to be balanced.

Hot flashes

Hot flashes, described as sudden sweating and facial discomfort, affect up to 80% of patients treated with ADT.[58] For some patients, these flashes are debilitating while for others they are simply a nuisance. Conservative management is initially the first recommendation for management of hot flashes including limiting exposure to potential triggers (i.e.: heating, or spicy foods).[59] Various medications are available to reduce the frequency and severity of hot flashes. A randomized controlled trial demonstrated that venlafaxine, cyproterone acetate and medroxyprogesterone all led to improvements within 1 month of initiation and can be considered for bothersome symptoms.[60]

Conclusion

ADT is an important treatment modality in the management of prostate cancer. However, it is known to be associated with a variety of potential negative sequalae. The impact of ADT on bone health, metabolic syndrome risk, cardiovascular disease risk, sexual function and the development of hot flashes has been illustrated. Strategies for mitigating adverse side effects are available but require a wide range of expertise to do so effectively. A model of collaborative care that includes a patient and his partner, his urologist, radiation oncologist and family physician can help to optimize outcomes in treating men with prostate cancer. □

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