Androgen Deprivation Therapy for Prostate Cancer

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Context Prostate cancer is the most common nonskin cancer and second most common cause of cancer mortality in US men. Androgen deprivation therapy (ADT), specifically surgical or medical castration, is the first line of treatment against advanced prostate cancer and is also used as an adjuvant to local treatment of high-risk disease.

Objective To review systematically the evidence on the risks and benefits of ADT for prostate cancer as well as clinical management of its adverse effects.

Evidence Acquisition We performed MEDLINE searches of English-language literature (1966 to March 2005) using the terms *androgen deprivation therapy*, *hormone treatment*, and *prostate cancer*. We reviewed bibliographies of literature to extract other relevant articles. Studies were selected based on clinical pertinence, with an emphasis on controlled study design.

Evidence Synthesis Androgen deprivation therapy is effective for palliation in many patients with advanced prostate cancer and improves outcomes for high-risk patients treated with radiation therapy for localized disease. Although patients with increasing prostate-specific antigen levels after local treatment without metastatic disease frequently undergo ADT, the benefits of this strategy are not clear. Adverse effects of ADT include decreased libido, impotence, hot flashes, osteopenia with increased fracture risk, metabolic alterations, and changes in cognition and mood.

Conclusions Androgen deprivation therapy has clear roles in the management of advanced prostate cancer and high-risk localized disease. The benefits of ADT in other settings need to be weighed carefully against substantial risks and adverse effects on quality of life.

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Androgen deprivation therapy (ADT; herein defined as medical or surgical castration) is the cornerstone treatment of advanced prostate cancer. In 1941, Huggins and Hodges[1] first noted the beneficial effects of castration and injection of estrogens in patients with metastatic prostate cancer. The biological basis of the effect of ADT, the almost ubiquitous expression of the androgen receptor in prostate cancer, and growth dependence on the androgen receptor later became clear.

Today, in addition to its well-established role in treating patients with metastatic disease, ADT is sometimes used to treat patients with increasing prostate-specific antigen (PSA) levels after local treatment, even without radiographic or other evidence of metastatic disease. Androgen deprivation therapy is also used as adjunct therapy for men undergoing radiation therapy for high-risk localized disease (TABLE 1). Despite frequently dramatic and sustained responses of many patients to ADT, treatment exposes patients to a host of important adverse effects (TABLE 2). We sought to systematically review existing evidence regarding the benefits and risks of ADT in contemporary management of local and metastatic prostate cancer.

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EVIDENCE ACQUISITION

We performed MEDLINE searches of the English-language literature (1966 to March 2005) using the terms *androgen deprivation therapy*, *hormone treatment*, and *prostate cancer*. Relevant bibliographies of literature were manually reviewed for additional material. In evaluating the benefits of ADT, phase 3 randomized trial data were emphasized. On review of clinical trials, clinical end points of focus, in decreasing order of importance, were survival benefit, radiographic progression-free survival, and rising PSA level. Further information was obtained in oral and abstract form at the 2005 Prostate Cancer Symposium meeting, Orlando, Fla, and the 2005 American Society of Clinical Oncology meeting, Orlando, Fla. Published guidelines from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology were also reviewed.

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EVIDENCE SYNTHESIS

Medical vs Surgical Castration for Androgen Ablation

Orchiectomy is a relatively simple procedure with minor surgical risks.[12] Despite its low physical morbidity, orchiectomy has fallen out of favor given its psychological impact and viable medical alternatives for androgen deprivation.[13]

Medical castration with gonadotropin-releasing hormone agonists (GnRH-As) in prostate cancer patients was first reported in 1982.[14] Leuprolide and goserelin are 2 commonly used GnRH-As and are administered in the form of 1-, 3-, 4-, and 6-month depot injections, as well as 12-month subcutaneous implants. Endogenous GnRH is physiologically released in a pulsatile manner from the hypothalamus and is directed to the anterior lobe of the pituitary (FIGURE). In response, luteinizing hormone is released from the pituitary, which in turn stimulates testosterone production in the testes. Long-term treatment with GnRH-A supplants the effect of physiologically pulsatile endogenous GnRH and is thought to down-regulate its receptors in the pituitary gland, leading to castration levels of testosterone within 3 weeks.[15]

It is well recognized that GnRH-As initially cause a surge in testosterone and can cause a "flare" reaction in patients with metastatic prostate cancer. This is due to an acute stimulation of prostate cancer growth by elevated levels of testosterone. A placebo-controlled trial has shown that androgen receptor antagonists lower the amount of bone pain with initiation of GnRH-A therapy for patients with metastatic prostate cancer.[16] To prevent flare reactions, some recommend that patients with metastatic disease start with an androgen antagonist prior to initiation of treatment with a GnRH-A and continue for 2 to 4 weeks to block the effect of the testosterone surge on peripheral androgen receptors.[17]

Gonadotropin-releasing hormone antagonists may alternatively be used for medical castration and do not cause a testosterone surge, but they have a 3.7% incidence of anaphylaxis.[18] Gonadotropin-releasing hormone antagonists are indicated for palliative treatment of men with advanced symptomatic prostate cancer, in whom GnRH-A therapy alone is not appropriate because of an initial increase in testosterone, who refuse surgical castration, and who have one or more of the following: (1) risk of neurological compromise due to metastases; (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease; or (3) severe bone pain from skeletal metastases persisting with narcotic analgesia use.[18]

In principle, it is important to achieve serum testosterone concentrations as

Table 1. Benefit of ADT for Stages of Prostate Cancer

Prostate Cancer Stage	Source	Study Results: Outcome	Control Arm, % (95% CI)	Early-ADT Arm, % (95% CI)	*P* Value
Advanced	MRC,[2] 1997	Decrease in rate of cord compression	4.9	1.9	<.025*
		Decrease in rate of ureteral obstruction	11.8	7.0	<.025*
		Decrease in extraskeletal metastasis	11.8	7.9	<.05*
		Decrease in rate of pathologic fracture	4.5	2.3	NS
Patients with local treatment for high-risk or locally advanced disease	Bolla et al,[3] 1997, and Bolla et al,[4] 2002	Increase in 5-y survival	62 (52-72)	78 (72-84)	.0002
	Pilepich,[5] 2003	Increase in 10-y survival	38	53	<.004
	D'Amico et al,[6] 2004†	Increase in 5-y survival	78 (68-88)	88 (80-95)	.04
	Messing et al,[7] 1999, and Messing et al,[8] 2003	Increase in 10-y survival	49.0	72.4	.025

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; MRC, Medical Research Council Prostate Cancer Working Party Investigators Group; NS, nonsignificant (value not reported in original study).
*Two-sided *P* values.
†This trial also included patients not at high risk.

Table 2. Selected Adverse Effects of ADT and Evidence for Treatment

Adverse Effect	Source	Treatment for Adverse Effect	Study Results: Outcome	Control Arm	Intervention Arm	*P* Value
Hot flashes	Loprinzi et al,[9] 1994	Megestrol acetate*	Reduction in hot flashes	20%	74%	<.001
Osteoporosis and increased risk of fracture	Smith et al,[10] 2001	Pamidronate	BMD change	Decrease of 1.8%-8.5%	No change	≤.02
	Smith et al,[11] 2003	Zoledronic acid	BMD change	Decrease of 2.2%	Increase of 5.6%	<.001

Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density.
*May cause disease progression.

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low as possible for ADT to minimize stimulation of prostate cancer cells. Serum testosterone concentrations that correspond to castration levels have generally been set at less than 50 ng/dL (1.7 nmol/L), given the known variability of values in reference laboratories.[19] However, most men achieve levels below 20 ng/dL (0.7 nmol/L) after orchiectomy, and it has been suggested that castration levels should be redefined to reflect this threshold.[20]

Antiandrogens and Inhibitors of Steroid Synthesis

There are several other classes of agents that are used clinically to block the effects of androgens (Figure). Androgen receptor antagonists such as flutamide, bicalutamide, and nilutamide are often used either alone or in combination with castration to block the effects of androgens. Ketoconazole and other adrenal ablating drugs are used to inhibit cytochrome P450 enzymes, which are required for the synthesis of androgens and other steroids.

Testosterone released from the testes is converted to dihydrotestosterone, a more potent activator of the androgen receptor than testosterone. Finasteride inhibits 5α-reductase, the enzyme responsible for this conversion. Finasteride has no defined role in the standard care of patients with prostate cancer but may have a role in prevention.[21]

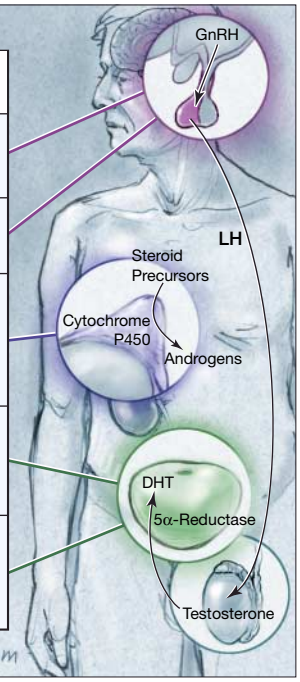
Benefits of ADT

Advanced Prostate Cancer. The first large randomized controlled trial to address the efficacy of orchiectomy in advanced prostate cancer was the Veterans Administration Co-operative Urological Research Group (VACURG) I study, which also included an arm with no treatment.[22,23] After 9 years, all men with metastatic disease in the control arm were treated with androgen ablation. Therefore, this trial may be best described as a comparison of early vs late ADT.[24] Survival curves for men in these arms were essentially equivalent, suggesting that there is no survival advantage to early treatment with ADT. This trial did not address any palliative end points.

The Medical Research Council conducted a randomized trial of early vs late ADT in patients with locally advanced disease or asymptomatic metastatic disease. Two hundred fifty-seven (71%) of 465 patients in the deferred-treatment arm died of prostate cancer vs 203 (62%) of 469 patients in the immediate-treatment arm ($P=.001$). Fifty-five men (11.8%) in the deferred arm and 37 (7.9%) in the immediate-treatment arm had extraskeletal metastases ($P<.05$). The number of patients with pathological fracture were 21 (4.5%) in the deferred-treatment arm vs 11 (2.3%) in the immediate-treatment arm (not statistically significant). Twenty-three patients (4.9%) in the deferred-treatment arm vs 9 (1.9%) in the immediate-treatment arm had spinal cord compression ($P<.025$). Fifty-five (11.8%) and 33 (7.0%) patients had ureteral obstruction, respectively ($P<.025$). Bone pain and other quality-of-life measures were not reported. An important

Figure. Hormonal Interventions and Endocrine Axis in Prostate Cancer

Drug Class	Drugs	Site of Action	Mechanism of Action	Comments/Risks
Gondatropin-Releasing Hormone (GnRH) Agonists	Leuprolide Goserelin	Anterior Pituitary Gland	Decreases Release of LH Through Down-regulation of GnRH Receptors	Testosterone Surge
GnRH Antagonists	Abarelix*	Anterior Pituitary Gland	Directly Inhibits GnRH Receptors	Anaphylaxis
Adrenal Ablating Drugs	Ketoconazole	Adrenal Gland	Decreases Androgen Synthesis From Steroid Precursors Through Inhibition of Cytochrome P450 Enzymes	Administration Requires Steroid Supplementation to Prevent Adrenal Insufficiency
Androgen Receptor Antagonists	Flutamide Bicalutamide Nilutamide	Prostate Gland	Inhibits Androgen Receptor Ligand-Binding Domain Through Competitive Binding	Gynecomastia, Increased Liver Transaminases, and Mastodynia
5α-Reductase Inhibitors	Finasteride	Prostate Gland	Decreases Conversion of Testosterone to DHT Through Inhibition of 5α-Reductase	No Defined Role in Standard Care of Prostate Cancer



DHT indicates dihydrotestosterone and LH, luteinizing hormone. Asterisk indicates no longer available for new patients in the United States. Illustration based on original concept by Lydia Kibiuk.

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note is that this study has been criticized because many of these patients died before starting ADT.[2]

The efficacy of medical vs surgical castration for advanced prostate cancer has been addressed. Ten randomized trials of GnRH-A compared with orchiectomy have been conducted and were systematically evaluated in a previously published meta-analysis.[25] All of these trials found equivalence between GnRH-A and orchiectomy in terms of survival, progression-related outcomes, and time to treatment failure.

Advanced prostate cancer almost always becomes androgen independent after castration. The duration of response after ADT in the metastatic setting is typically 14 to 20 months.[26,27] Secondary hormone treatment with androgen receptor antagonists or ketoconazole is often used when prostate cancer progresses after ADT.[28]

In summary, in the setting of advanced prostate cancer, ADT—whether surgical or medical—provides important quality-of-life benefits, including reductions of bone pain,[29] pathological fracture, spinal cord compression, and ureteral obstruction. However, it is not clear whether there is an improvement in long-term survival.

ADT Adjuvant to Radiation Therapy or Prostatectomy. Several phase 3 randomized trials have shown a benefit in overall survival when comparing radiation therapy alone to radiation therapy plus ADT for patients with locally advanced (ie, extracapsular or node-positive) disease. The European Organisation for Research and Treatment of Cancer conducted a phase 3 trial in 412 patients with locally advanced disease, randomizing the patients to GnRH-A plus radiation therapy vs radiation therapy alone. In the combination arm, ADT was started on the first day of radiation and continued for 3 years.[3,4] Overall survival at 5 years was 78% for combined treatment and 62% ($P<.001$) for radiation therapy alone. Among surviving patients, 74% and 40% were free of disease at 5 years in the combined treatment and radiation-only groups, respectively ($P<.001$).

In the Radiation Therapy Oncology Group Trial 85-31, a GnRH-A was started in the last week of radiation therapy and continued indefinitely for patients with evidence of extracapsular disease or regional lymph node involvement.[30,31] A recent analysis[5] of this study found an improvement in overall survival favoring the ADT arm (estimated 10-year absolute survival of 53% vs 38%; $P<.004$), and a retrospective subset analysis of this trial suggested a significant improvement in survival favoring the ADT arm among patients with involved regional nodes.[32] D'Amico et al[6] conducted a randomized controlled trial of 3-dimensional conformal radiation therapy (3D-CRT) with or without 6 months of GnRH-A therapy in 206 patients with prostate cancer with a Gleason score of at least 7, evidence of extraprostatic disease, or a PSA level of at least 10 ng/mL. The estimated 5-year survival of the combined therapy group was 88% vs 78% in the 3D-CRT-only group ($P=.04$). Survival free of salvage ADT was 82% and 57% in the combined-therapy and 3D-CRT groups, respectively ($P=.002$). It is also important to note that a critique of adjuvant ADT studies for high-risk (ie, stage ≥T2c, PSA >20 ng/mL, or Gleason score ≥8) or locally advanced disease is that these trials have no ADT-only arm.[4] The NCCN recommends hormone therapy plus radiation therapy for patients with high-risk disease.[17]

Messing et al[7] conducted a prospective, randomized trial examining the effect of early ADT on outcomes for men with pelvic lymph node involvement who had undergone radical prostatectomy. Seven (15%) of 47 men in the early-ADT arm had died after a median follow-up of 7.1 years vs 18 (35%) of 51 men in the observation arm ($P=.02$). Furthermore, 36 men (77%) in the early-ADT arm were alive and free of disease with undetectable PSA levels vs 22 (43%) in the observation arm ($P<.001$).

Messing et al[7,8] conducted a prospective randomized trial examining the effects of early ADT on outcomes for men with pelvic lymph node involvement who had undergone radical prostatectomy. Thirteen (28%) of 47 men in the early-ADT arm had died after a median follow-up of 10 years vs 26 (51%) of 51 men in the observation arm ($P=.025$).

Biochemical Failure. Biochemical failure is defined as a progressively increasing PSA level without radiographic metastatic disease after treatment for localized disease. A retrospective study of men with a rising PSA level after prostatectomy with no hormone treatment revealed a median actuarial time to metastasis of 8 years after PSA elevation.[33] Only 103 (34%) of 304 men in that study developed clinically apparent metastases. However, only 53% of the subset of men with a Gleason score of 8 to 10 and biochemical recurrence within 2 years of prostatectomy were metastasis-free at 3 years.

Although many men with biochemical failure are treated with ADT, there are no data currently available from prospective trials to address a possible benefit in terms of disease progression or survival.[34] Given that there is no definitive survival advantage to early ADT in advanced prostate cancer, there may be no compelling reason to treat most men with biochemical failure. However, given the survival advantage of adjuvant ADT for men with locally advanced or high-grade disease and earlier time to metastasis in men with high-grade tumors or aggressive features, there may be a potential benefit in treating this subset of men who have biochemical failure. This matter is subject to debate, and ascertainment of the benefit of ADT for biochemical failure after prostatectomy or radiation therapy awaits data from prospective studies.

Adverse Effects of ADT

Hot Flashes. Hot flashes can significantly affect quality of life for men undergoing ADT. Up to 80% of patients undergoing treatment with GnRH-A report hot flashes and up to 27% report this as the most troublesome adverse effect.[35] Most intervention studies for hot flashes have evaluated treatments in breast cancer patients taking tamox-

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ifen or women who are postmenopausal.[36]

A randomized, double-blind, placebo-controlled trial of megestrol acetate for prevention of hot flashes in women with a history of breast cancer and men undergoing ADT for prostate cancer showed a reduction in hot flashes in 74% of the megestrol group and 20% of the placebo group by intention to treat ($P<.001$).[9] The efficacy of megestrol was similar in men and women. However, PSA levels have been reported to increase in men who commence megestrol while receiving ADT and decline with discontinuation of megestrol.[37,38] Although antidepressants are sometimes used and have been evaluated in small pilot trials,[39,40] we could find no large-scale placebo-controlled trials demonstrating efficacy in men undergoing ADT.

Skeletal Complications. Several prospective trials have established that bone mineral density (BMD) is significantly decreased in men receiving ADT compared with a control group. Notably, these losses surpass bone loss in women who are in early menopause.[41] A recent study of more than 50 000 men from the Surveillance, Epidemiology and End Results program (SEER) and Medicare databases compared the risk of fracture in men with a diagnosis of prostate cancer who were treated with ADT vs those not receiving ADT.[42] Men who were treated with ADT had an increased risk of fracture starting 1 year after diagnosis. The risk of fracture increased with an increase in the number of doses of GnRH-A received. The number needed to harm for an occurrence of fracture 1 to 5 years after diagnosis was 28 for men treated with GnRH-A and 16 for men treated with orchiectomy.

Therapeutic intervention to prevent skeletal complications for men treated with ADT has been examined in both nonmetastatic and metastatic clinical settings. In a randomized trial of 47 men with nonmetastatic prostate cancer, GnRH-A alone was compared with GnRH-A plus 60 mg of pamidronate given every 12 weeks. Men in the GnRH-A-only arm had a mean decrease in lumbar, trochanter, total hip, and trabecular lumbar spine BMD of 3.3% ($P<.001$), 2.1% ($P=.003$), 1.8% ($P=.005$), and 8.5% ($P=.02$), respectively, after 48 weeks. Mean BMD did not change significantly in the GnRH-A plus pamidronate group.[10] In a multicenter, double-blind study, 106 men with nonmetastatic prostate cancer who were starting ADT were randomized to receive placebo vs 4 mg of zoledronic acid every 3 months for 1 year. Mean lumbar spine BMD decreased in the placebo group by 2.2%, whereas BMD increased by 5.6% in the zoledronic acid group ($P<.001$).[11] A randomized, placebo-controlled trial of zoledronic acid in patients with androgen-independent metastatic prostate cancer showed a significant decrease in skeletal-related events in the zoledronic acid arm (33% vs 44%; $P=.02$).[43]

Men receiving or starting ADT should be evaluated for risk of osteoporosis. These risks include family history of osteoporosis, low body weight, prior fractures, excessive alcohol use, smoking, glucocorticoid use, low vitamin D levels, and other medical comorbidities. All men should start calcium and vitamin D supplementation. Baseline BMD should be determined. Routine use of bisphosphonates in patients undergoing ADT is not recommended unless there is documented osteoporosis or androgen-independent prostate cancer with skeletal metastasis. Men who smoke or have excessive alcohol consumption should be urged to abstain.[44,45]

Sexual Function. Testosterone plays an important role in normal male sexual function. Decreasing serum testosterone can have a significant negative impact on quality of life for patients treated with ADT. Although erectile dysfunction is not uncommon after radical prostatectomy, men who undergo ADT have a further decline in ability for sexual intercourse and a decrease in sexual desire compared with men who are not treated with ADT.[46]

The Prostate Cancer Outcomes Study of the SEER program examined quality-of-life outcomes for 431 men with all stages of prostate cancer who were treated with ADT and no other treatment within 1 year of initial diagnosis. The impact on sexual function of treatment with a GnRH-A or an orchiectomy was noted. Men reporting no sexual interest increased from 27.6% to 63.6% after orchiectomy and 31.7% to 58.0% after GnRH-A. Men who achieved no erections increased from 35.0% to 78.6% after orchiectomy and 37.9% to 73.3% after GnRH-A. Men with no sexual activity increased from 47.9% to 82.8% after orchiectomy and 45.0% to 80.2% after GnRH-A. Surprisingly, despite the cosmetic effects and psychological impact of orchiectomy, GnRH-A and orchiectomy had similar effects on sexual function.[47] Although phosphodiesterase type 5 inhibitors are an option, there has been no study specifically evaluating these drugs in men treated with ADT. Penile implants, vacuum devices, and intracavernosal injections of prostaglandin are other available options.[36]

Metabolic Changes. Serum testosterone levels have a negative correlation with fat mass and a positive correlation with muscle mass. Testosterone replacement has been shown to increase lean body mass in men who are deficient in testosterone because of age or chronic disease states.[48]

Three prospective studies have compared body composition and metabolism in cohorts of men with prostate cancer before ADT and 6 to 12 months after ADT.[49-51] These studies have noted increases in body mass index of 1.6% to 2.4%. Among 35 men in 1 study, fat body mass increased 10% to 20% in 7 men (20%), 20% to 50% in 8 men (22.8%), and more than 50% in 5 men (14.3%). Lean body mass was found to decrease between 2% and 5% in 8 men (22.8%) and greater than 5% in 7 men (20%).[50] Both studies that examined total cholesterol and triglycerides found a significant increase in both of these measures.[49,51] One of these studies noted increases in high-density lipoproteins, low-density lipoproteins, total cholesterol, and triglycerides of 11.3% ($P<.001$), 7.3% ($P=.05$), 9.0% ($P<.001$), and 26.5% ($P=.01$).[49] The only study that examined changes in

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fasting glucose levels noted a significant increase after ADT.[51] A retrospective analysis of men receiving ADT suggests that such metabolic changes lead to increases in Hb_{A1c}.[52]

A caveat for all of these studies is that they are comparisons of the same patients before and after ADT and, therefore, lack a control group. Nonetheless, these data are consistent with the physiologic changes that have been recognized in other forms of testosterone deficiency. The combination of increasing fat mass, increasing cholesterol, and glucose intolerance may be related to what is recognized as the metabolic syndrome. While metastatic prostate cancer provides a compelling reason for ADT, the impact of negatively modifying cardiovascular risk factors with ADT in other clinical settings for prostate cancer patients, who have a median age of 70 years, should, we believe, be measured carefully, especially in men with biochemical recurrence in the absence of data on survival.

Cognitive and Mood Changes. There is conflicting literature on the issue of cognitive function changes in men undergoing ADT. A study that randomized 82 men to GnRH-A vs close clinical monitoring suggests that there may be worsening on some tests of attention and memory.[53] However, a second study does not suggest any cognitive impairment in men being treated with ADT but, rather, noted an improvement in object recall.[54] A more recent prospective study associates declines in verbal fluency, visual memory, and visual recognition with declines in estradiol induced by ADT.[55]

A quality-of-life study of 144 men given a choice of immediate or deferred ADT found significantly worse scores for fatigue and psychological distress for the men receiving ADT.[56] Men with prostate cancer surveyed at Massachusetts General Hospital were found to have 8 times the national rate of depression. However, this was not associated with ADT.[57]

Other Changes. Normocytic, normochromic anemia is seen in many patients receiving ADT. Strum et al[58] prospectively evaluated patients receiving combined androgen blockade. They found a hemoglobin decrease of at least 10% in 90% of their patients and a hemoglobin decrease of at least 25% in 13% of patients. Anemia may be a contributing factor to fatigue that is associated with ADT.

Gynecomastia occurs in 1% to 16% of men treated with ADT. Treatment options include breast irradiation, surgery, and tamoxifen. Surgical therapies are also an option.[59] Other adverse effects of ADT include dry eyes, body hair loss, and vertigo.[36]

CONTROVERSIES

Combined Androgen Blockade

Despite medical or surgical castration, continued release occurs of a lower level of androgens, mainly from the adrenal glands. A long-standing debate exists on the use of combined androgen blockade, which is treatment with castration along with an androgen receptor antagonist. An earlier study comparing daily injections of a GnRH-A vs GnRH-A plus an androgen antagonist found survival benefit for combined androgen blockade.[26] However, a second large, randomized study found no survival benefit for combined androgen blockade when surgical castration was used.[27] A meta-analysis of 27 randomized trials found a slight but significant 5-year survival benefit for combined androgen blockade.[60] The number of patients needed to treat with combined androgen blockade to prevent 1 death is estimated at 20 to 100.[12] It is estimated that the increased costs amount to $1 million per quality-adjusted life-year.[12]

Intermittent Androgen Blockage

Some have argued that intermittent ADT will delay progression to androgen independence compared with sustained ADT and that a testosterone increase when ADT is not in use decreases adverse effects. Although phase 3 trials are under way, there currently are no data from prospective randomized trials, and the American Society of Clinical Oncology considers intermittent androgen blockade to be experimental.[12]

Antiandrogen Monotherapy

Nonsteroidal antiandrogen monotherapy has a less severe adverse-effects profile than that of ADT, making it a potential alternative. In a meta-analysis comparing bicalutamide and castration, overall survival with bicalutamide monotherapy was statistically not worse than that with castration.[25] The American Society of Clinical Oncology states that monotherapy with a nonsteroidal antiandrogen may be discussed as an alternative to ADT, but steroidal antiandrogens (currently not approved in the United States) should not be offered as monotherapy.[12]

CONCLUSIONS

Androgen deprivation therapy is the most widely used systemic treatment for prostate cancer. In the metastatic setting, ADT has clear quality-of-life benefits but has not been shown to have survival benefit. Patients receiving local treatment with radiation therapy for high-risk disease have proven survival benefit. However, the role and benefit of ADT in biochemical failure after local therapy is unclear.

Adverse effects of ADT often mimic testosterone deficiency due to other causes. When anticipated prior to or early in ADT, some adverse effects, such as bone loss, can be prevented. Adverse effects, such as hot flashes and sexual effects, can significantly affect quality of life. Metabolic changes also occur, some of which are risk factors for cardiovascular disease. Clearly, further study is required to help physicians carefully weigh the benefits against the morbidity associated with ADT and to optimize the management of adverse effects.

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