Preventing and Treating the Complications of Hormone Therapy

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Hormonal manipulation in the form of androgen-deprivation therapy for prostate cancer was introduced by Huggins and Hodges in 1941 and resulted in a Nobel Prize in 1966. Hormonal therapy initially had been used in metastatic prostate cancer, but the indications have been expanded including failed local therapy, locally advanced prostate cancer, and neoadjuvant or adjuvant therapy in high-risk localized prostate cancer. In view of the magnitude of the problem of prostate cancer and relatively frequent use of hormonal manipulation, it is important for clinicians to be aware of common side effects, prevention, and treatment to improve quality of life and reduce morbidity and mortality in patients with prostate cancer. This review focuses on the common side effects of hormonal treatment such as osteoporosis, anemia, hot flashes, erectile dysfunction, muscle wasting, gynecomastia, decline in cognitive function, depression, increase in body fat and metabolic changes, and their prevention and treatment.

Introduction

Hormonal manipulation in the form of androgen-deprivation therapy for prostate cancer was introduced by Huggins and Hodges [1] in 1941 and resulted in a Nobel Prize in 1966. Prostate cancer is the second most commonly diagnosed cancer in men in the United States after skin cancer and the second leading cause of death in men after lung cancer [2]. Hormonal manipulation in the form of androgen deprivation initially had been done by Huggins and Hodges [1]. The different types of androgen-deprivation are orchiectomy, use of estrogenic compounds, medical castration in the form of luteinizing hormone-releasing hormone analogs (LHRH), and blocking androgen action with antiandrogens. Different modes of androgen deprivation include continuous hormonal therapy, intermittent therapy, and monotherapy with antiandrogen, maximal androgen blockade combining LHRH analog with antiandrogen and the use of antiandrogen with 5-α reductase inhibitors. These different techniques are being evaluated to reduce the side effects of continuous androgen deprivation. Hormonal deprivation initially was confined to advanced prostate cancer not amenable to curative local therapy in the form of radiotherapy or radical prostatectomy. Indications have been expanded because there are some data showing that in patients undergoing radiotherapy, the use of concomitant hormonal manipulation improves outcome in high-risk patients [3]. Hormonal manipulation also is being evaluated in patients with positive pelvic lymph nodes after radical prostatectomy [4]. A Medical Research Council trial also has shown that early hormonal manipulation has reduced complications and prolonged survival in metastatic prostate cancer [5]. Hormonal manipulation also is being evaluated in patients with biochemical recurrence after radical prostatectomy. This review is a compilation of complications of hormonal manipulation, their prevention, and treatment. The common side effects of androgen deprivation are listed in Table 1.

Side Effects

Osteoporosis

Development of skeleton and structural anatomy of bone differs in men and women. As a normal part of aging, bone loss in men generally is slower and occurs less than in women [6]. Studies have shown that decrease in bone density is approximately 0.5% to 1% per year in elderly men [6]. Bone mineral density (BMD) is used to define osteoporosis and osteopenia. The commonly used technique to assess BMD is dual energy X-ray absorptiometry. A disadvantage of this technique is that it measures density per area, not volume, and it tends to overestimate values because vertebral bodies have more cross-sectional area in men. The other technique used is quantitative computerized tomography, which analyzes trabecular bone and is very sensitive and accurate; however, its increased sensitivity sometimes may overestimate the values. Usual definition of osteoporosis is 2.5 standard deviations less than young healthy subjects with regard to bone density [7,8]. Fractures resulting from osteoporosis are an important health problem in men. Several studies have shown that mortality rates after hip fractures are higher in men than in women [9]. The relationship between androgen activity reduction and osteoporosis was demonstrated initially in 1989 by a study comparing bone density in patients who

Table 1. Complications of hormonal treatment

Complication	Percentage
Osteoporosis	1% to 3%
Anemia	90% has 10% drop in hemoglobin; 13% has > 25% drop in hemoglobin
Impotence	50% to 100%
Gynecomastia	13% to 70%
Fatigue	13%
Hot flashes	55% to 80%
Gastrointestinal side effects	22%
Decline in cognitive function	> 50%
Muscle wasting	Common
Depression	Common
General weekness	Common

underwent orchiectomy with healthy control subjects. There was an increase in incidence of fractures by 2.5 times [10]. Retrospective and prospective studies have looked at the association between osteoporotic fractures and androgen ablation. In one retrospective study, there was a 14% incidence of fractures in a group who had orchiectomy compared with control subjects, who had an incidence of 1% [11]. In another retrospective study in which a chart review was performed, patients with prostate cancer who had androgen deprivation had a fracture-free survival of 96% at 5 years, but fell to 80% at 10 years [12]. Prognostic variables that conferred benefit were increased body mass index and black race. The negative variable was longer duration of hormonal manipulation. Studies done prospectively have shown that medical or surgical castration causes 5% to 10% loss in BMD [13,14,15•]. One study also showed that patients with prostate cancer had osteoporosis even before starting hormonal manipulation. Up to 34% of patients had osteoporosis of the hip and spine as shown by dual energy X-ray absorptiometry and 63% had it shown on quantitative computed tomography of the lumbar spine [16•]. Metabolic activity of bone is influenced by sex hormones. Research has shown that in inhibition of estrogens and testosterone by leuprolide injections when followed by replacement of estrogen or testosterone alone, or both, or neither, estrogen proved to be more important than testosterone in the maintenance of bone density [17]. Although testosterone supplementation in hypogonadal men increased BMD by 15% to 25% [18], this option cannot be recommended in men with prostate cancer. Lifestyle modification, including smoking cessation, decreasing alcohol intake, resistance exercises, and adequate supplementation of calcium up to 1200 mg and vitamin D up to 400 IU daily, is advised (Table 2). Other treatment options include use of bisphosphonates and estrogens. The three different bisphosphonates being used are alendronate, pamidronate, and zoledronate. The initial drug approved by the US Food and Drug Administration for osteoporosis was alendronate, which can be administered orally. Precautions include taking it while in an erect position and on empty stomach and having the head elevated for 30 minutes. Side effects include esophagitis, abdominal pain, and gastroesophageal ulceration. Alendronate was shown to increase BMD at the lumbar spine and femoral neck in patients with prostate cancer who were not undergoing hormonal deprivation [19]. Pamidronate and zoledronate are available only as intravenous preparations. Two randomized groups of patients with prostate cancer without bone metastases were administered leuprolide alone or leuprolide and pamidronate 60 mg every 12 weeks. The group receiving pamidronate maintained bone density while the other group had significant loss of density of 3.3% at the lumbar spine, 2.1% at the trochanter, and 1.8% at the hip [20•]. Zoledronic acid was shown to reduce skeletal-related events in patients with prostate cancer and bone metastases. The dose used was 4 mg administered intravenously every 3 weeks [21]. This study also showed reduction in pain resulting from skeletal metastases. It also was shown to increase bone density in a prospective, randomized trial in patients receiving LHRH analogs [22••]. Adverse effects of bisphosphonates are anemia, constipation, fever, reactions at intravenous sites, and hypophosphatemia. Higher doses and rapid administration of zoledronic acid was associated with renal failure and mandates creatinine monitoring. Some screening recommendations include determining BMD before the start of androgen deprivation, at 1 year after beginning therapy, and possibly once 2 years thereafter. Estrogens were used in the past for the treatment of prostate cancer; in one study, BMD was maintained in the group who had orchiectomy with estrogen and it significantly decreased in the group who underwent orchiectomy alone [23].

Hot flashes

Hot flashes are common side effects of hormonal manipulation. Typical manifestation of a hot flash is feeling of warmth in the face, neck, upper chest, and back, which may be associated with flushing of face and nausea. The duration can vary from a few seconds to 1 hour. Hot flashes can be provoked by heat or stress or can occur spontaneously and may be accompanied by sweating and disturbed sleep. Their intensity can vary from mild to severe and causing incapacitation. The frequency of hot flashes during hormonal manipulation varies from 55% to 80% and they usually do not resolve over time [24]. The mechanism of hot flashes is thought to result from a lack of testosterone endogenous peptide secretion increase, which in turn stimulates the nearby hypothalamic thermoregulatory center, resulting in a feeling of warmth [25]. Therapy of hot flashes is similar to the treatment of postmenopausal symptoms in women. Various treatments include estrogens, progestins, clonidine, antidepressants, cyproterone acetate, and alternative forms of therapy such as acupuncture, soy, and vitamin E (Table 3). Estrogens are

Table 2. Treatment and prevention of osteoporosis

Calcium supplementation
Vitamin D supplementation
Smoking cessation
Resistance exercise
Reduce alcohol and caffeine ingestion
Diethyl estradiol therapy
Use of antiandrogens alone
Alendronate
Pamidronate
Zoledronate

administered in the form of low-dose diethylstilbestrol, which improved symptoms in 75% to 90% of men. A side effect was tender gynecomastia in some studies and there was no cardiovascular mortality [25,26]. Transdermal estrogen also was used in some studies, with improvement noted in symptoms in 83% of the patients and was associated with gynecomastia and nipple tenderness [27]. One problem with the use of estrogens is that not every pharmacy compounds them. Megestrol acetate was shown in a double-blind, randomized trial to be effective in 85% of patients compared with 21% who received placebo. Peak effect was noticed after 2 to 3 weeks and there was residual post-therapy effect for several weeks [28]. The side effects noticed included a decrease in prostate-specific antigen (PSA) after stopping therapy, postulating an adverse effect on the prostate [29]. Antidepressant agents such as venlafaxine and fluoxetine have been useful. Venlafaxine at a 25-mg dose reduced hot flashes in more than 50% of men in a study. Side effects included nausea, constipation, anorexia, and dryness of mouth [30]. Medroxyprogesterone acetate was another drug that improved symptoms completely in more than 82% of patients in a study. Side effects include sexual dysfunction [31]. Clonidine was tried initially in the treatment of hot flashes, but randomized studies have shown that it provides no benefit [28]. Gabapentin, an analog of γ amino butyric acid used to treat epilepsy, also was helpful in some case studies. Its mode of action seems to be reduction of noradrenergic overactivity [32]. Cyproterone, a steroidal antiandrogen, also was shown to be effective in reducing hot flashes in 80% of patients in a study by Cervenakov *et al.* [33]. Side effects include increased cardiovascular risk and altered lipid profiles. Alternative therapies for hot flashes include acupuncture. Hammar *et al.* [34] performed a study that included seven men for whom twice a week therapy was used for 2 weeks in the induction phase and therapy was continued once a week for 10 weeks in the maintenance phase. There was a 70% improvement in symptoms noted by six of seven men at 10 weeks; at 3 months, improvement was up to 50%. Soy products also have shown some benefit in the treatment of hot flashes. In a study by Murkies *et al.* [35], 58 subjects were given soy flour or wheat (45 g daily) over 12 weeks. The group taking soy flour experienced a 40% reduction in the incidence of hot flashes compared with the wheat group, who had a 25% reduction. Another study that included 20 postmenopausal women showed a benefit of 45% with a soy supplement in the form of 50 mg of isoflavones compared with a 25% improvement in symptoms with placebo [36]. Side effects of soy may include nausea, bloating, and constipation. Some studies have suggested benefit from vitamin E in postmenopausal women, but a recent crossover trial of vitamin E and placebo, which included 120 women with breast cancer, showed a very similar reduction in the frequency of hot flashes: 25% versus 22%, respectively. However, a crossover analysis revealed a small but statistically significant decrease in the number of hot flashes, equivalent to one hot flash less daily compared with placebo [37]. Black cohosh supplements have been shown to be of benefit in postmenopausal symptoms in some studies in Germany [38]. However, a randomized study in the United States did not show any benefit in women with a history of breast cancer [39]. Other alternative agents used for reducing hot flashes include red clover supplements, ginseng, estrogen-like licorice, and turmeric [40,41].

Gastrointestinal side effects

Antiandrogen flutamide has significant gastrointestinal side effects such as abdominal pain, diarrhea, and constipation in up to 22% of patients [42•]. Flutamide also can produce hepato-toxicity in the form of abnormal liver function tests and even liver failure [43]. Serious consequences can be prevented through regular monitoring of liver function tests and discontinuation of antiandrogen when an abnormality develops.

Anemia

The type of anemia that develops as a result of hormonal deprivation therapy is normocytic normochromic. The etiology is caused by the lack of stimulation of erythroid stem cells by testosterone and dihydrotestosterone and deficiency of erythropoietin [44]. The study also showed that hemoglobin can fall within 1 month after starting therapy; up to 90% of patients showed a 10% decrease in hemoglobin and 13% of the patients experienced a 25% decrease in hemoglobin. The lowest hemoglobin level was reached by 5.8 months. Anemia tended to cause symptoms in 13% of patients and was worse in combined androgen blockade compared with the use of LHRH analogs alone. When patients on LHRH analogs had antiandrogen added, there also was an additional decrease in hemoglobin. In a study by Fonseca *et al.* [45], comparison of pre- and postoperative hemoglobin in orchiectomized patients showed a mean decrease of 1 to 2 G. Another study that involved a group of patients with benign prostatic hypertrophy who were placed on LHRH analogs showed a decrease in hemoglobin, which recovered after therapy was stopped [19]. Androgens stimulate renal

Table 3. Treatment of hot flashes

Estrogens
Clonidine
Venlafaxine
Gabapentin
Megestrol acetate
Medroxyprogesterone
Vitamin E
Acupuncture
Soy products
Black cohosh
Ginseng
Licorice

production of erythropoietin [46] and before availability of recombinant human erythropoietin, androgens were used to treat anemia secondary to renal failure and bone marrow failure. This form of anemia can be corrected with recombinant human erythropoietin.

Gynecomastia

Gynecomastia is a side effect that causes social embarrassment to a patient and can be painful. It can resolve after cessation of hormonal manipulation during the first year, but it tends to become permanent as a result of fibrosis and hyalinization in the breast [47]. The incidence of gynecomastia varies with the type of therapy. Estrogens have an incidence of 40% to 80%; antiandrogens, flutamide, bicalutamide, and nilutamide have an incidence of 40% to 70%, and LHRH analogs and maximal androgen blockade have an incidence of 13% [48]. Preventive and therapeutic options include radiotherapy to the breast and subareolar mastectomy. Radiation administered prophylactically has a good result in 89% of patients; however, if administered after gynecomastia is established, it does not cause regression, but can reduce pain [49]. Subareolar mastectomy performed simultaneously with orchiectomy effectively has prevented gynecomastia. The etiology of gynecomastia seems to be caused by an increase in the estrogen-androgen ratio seen in androgen deprivation. Breast pain was shown to be ameliorated by tamoxifen in several patients [50]. Aromatase inhibitors are another group of medications helpful for breast pain and enlargement in patients with prostate cancer [51].

Loss of muscle mass or sarcopenia

Loss of muscle mass or sarcopenia occurs with aging. It contributes to increased morbidity in the elderly by impairing physical performance and increasing the risk of falls [52]. The etiopathogenesis of sarcopenia is thought to result from a decrease in anabolic hormones such as testosterone and growth hormone and an increase in catabolic agents such as interleukin 1 and 6 and tumor necrosis factor [53]. A cross-sectional study was performed to evaluate positive prognostic factors for maintenance of muscle mass. Free testosterone levels proved to be the most important factor; other factors included degree of physical activity, insulin-like growth factor level, and cardiovascular disease [52]. Research has shown that giving testosterone to hypogonadal men improves muscle mass significantly [54]. Stone *et al.* [55] reported that patients receiving LHRH analog and cyproterone acetate showed an increase in fatigue and a decrease in muscle mass without a change in body mass index after 3 months of hormonal deprivation compared with baseline before the start of therapy [55]. Segal *et al.* [56•] reported that resistance exercise reduces fatigue and improves quality of life and muscular fitness in patients with prostate cancer receiving hormonal deprivation therapy.

Deterioration of cognitive function

Patients who have reached climacteric as a result of advanced age were shown to have improved cognitive function with testosterone replacement therapy, suggesting the role of androgens [57]. In a study looking at cognitive functioning in three groups of patients on LHRH analogue, cyproterone acetate and close observation showed impaired memory, concentration, and verbal skills in patients 6 months after therapy compared with baseline [58•].

Depression

Hormonal deprivation also has emotional consequences for the patients, including moodiness and short temper, crying with minimal provocation, and feeling depressed and anxious. Some of these side effects are noticed by the patient's partner [59]. Exercise, especially in the form of resistance, has helped to improve psychologic side effects in patients undergoing hormonal manipulation [56•].

Changes in body weight and lipid levels

Patients on hormonal deprivation tend to gain weight and experience an increase in fat [60]. In a study of combined androgen blockade, weight gain ranged from 3 to 15 kg; with LHRH analog therapy, up to 2.3 kg of weight gain occurred. The increase in weight was accounted for by an 11% increase in fat body mass and a 2.4% decrease in lean body mass. Furthermore, total cholesterol level increased by 9% and serum triglycerides increased by 26.5% [61]. The increase in weight associated with hormonal deprivation is very difficult to lose, even after discontinuing therapy [59]. Other changes associated with weight gain include increased appetite and increased insulin levels [62].

Another effect of androgen deprivation is loss of body hair and an increase in hair over scalp.

Sexual dysfunction

Sexual dysfunction is a common side effect of hormonal-deprivation therapy for prostate cancer. Bergman *et al.* [63] showed that men who underwent orchiectomy were more

likely to be impotent than those who had been treated with estrogens or radiotherapy. Research also has shown decreased sexual desire, arousal, and frequency of spontaneous early morning erections and increased difficulty in achieving and sustaining erections after starting LHRH analogs [64]. One study also showed that there is a decrease in frequency, degree of erection, length of erection, and rigidity in objective measurement of nocturnal penile tumescence before and after starting LHRH analog therapy. This study also showed a decrease in libido and frequency of intercourse [65]. Erectile dysfunction also is a common problem in men without prostate cancer. The Massachusetts Male Aging Study reported a prevalence of moderate to severe impotence in 34.8% of men between the ages of 40 and 70 years [66]. Androgen-deprivation therapy also reduces libido and men are told to expect erectile dysfunction while undergoing treatment. Although sildenafil, intraurethral alprostadil, intrapenile injections of vasoactive drugs, and vacuum-assist erection devices have been shown to be effective techniques in other causes of erectile dysfunction, they still are being evaluated in erectile dysfunction as a result of androgen deprivation. Testosterone replacement is the therapy of choice in impotent hypogonadal men, but generally has been considered to be contraindicated in prostate cancer.

Modifications of Androgen-deprivation Therapy

Modifications of androgen-deprivation therapy include intermittent androgen-deprivation therapy, use of antiandrogen monotherapy, and a combination of antiandrogen with the 5-α reductase inhibitor finasteride. These techniques are being evaluated to reduce the side effects of androgen-deprivation therapy, but their long-term efficacy is being studied. Intermittent hormonal therapy, which is being evaluated by the Southwest Oncology Group and the National Cancer Institute in two randomized studies, reduces side effects of androgen ablation and also reduces the cost of treatment. The advantages of intermittent androgen deprivation are to preserve sexual function, restore anemia, and maintain bone density during an off-cycle phase [67]. Other therapeutic maneuvers being used to reduce bone loss is bicalutamide monotherapy. A study by Smith *et al.* [68] has shown elevated biochemical markers of bone turnover in men receiving LHRH analogs, but not in men receiving bicalutamide monotherapy.

Miscellaneous Side Effects

Miscellaneous side effects of androgen-deprivation therapy include dry eyes, fatigue, vertigo, and stimulation of growth of meningiomas by LHRH analogs [69].

Conclusions

Androgen-deprivation therapy is being used very commonly in patients with prostate cancer and it is important for physicians to know the side effects of therapy and how to reduce morbidity and mortality and improve quality of life for patients. Patient counseling is an important aspect of management because patients should be made aware of the different side effects so that they understand the consequences of therapy. Simple measures such as exercise, consuming adequate calcium and vitamin D, and reducing smoking and alcohol intake should be emphasized because they have significant effects on the maintenance of the physical and mental well-being of the patients and reduce osteoporosis. Alternative therapies such as the use of intermittent androgen deprivation, antiandrogen monotherapy, and a combination of flutamide with finasteride need to be studied further to assess long-term efficacy and survival benefit. Improved knowledge of androgen-deprivation therapy by patients and physicians will help earlier identification of side effects, their prevention, and therapy.

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