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Advances in Management of Prostate Cancer

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전립선 암은 미국의 경우 남성에게서 발생빈도가 가장 높은 암이며, 폐암 다음으로 높은 cancer death를 보이고 있다. 우리나라에서도 매 해 진단을 받는 환자 수가 증가하는 추세에 있으며, 이들 중 대부분은 말기로 진단을 받고 있다. 발생원인은 여러 가지 연구가 진행되고 있음에도 불구하고 확실히 밝혀지고 있지는 않은 상태이다 . 전립선 암은 다른 종류의 암에 비해 비교적 서서히 진행되는 한편 다른 암들과 마찬가지로 초기에는 자각증세가 거의 없기 때문에 조기 진단의 중요성이 강조된다. 이 종설에서는 전립선 암의 병기분류하는 방법과, 그에 따른 치료가 어떻게 달라지며, 최근에 시도되고있는 치료방법으로 어떤 것들이 있고 효과는 어느 정도 인가를 알아보도록 하겠다.

Introduction

According to the American Cancer Society estimation, approximately 180,000 men were diagnosed with prostate cancer in 2000 in the United States and 32,000 men will die each year due to prostate cancer. Throughout the 1990's the incidence of prostate cancer rose dramatically, however, over the past few years there has been a significant downward turn. The increase in the prevalence of prostate cancer is presumably due to the better awareness of the disease, increased longevity of the population, improved screening techniques and environmental factors.[1] In addition, the stage of presentation has been shifted form advanced to more early stage prostate cancer. Although there are still some who question the value of screening, because of the fear of diagnosing and treating individuals who have a indolent form of the disease; it is hard to argue with the fact that mortality since 1993 has declined by 27%.

Histologic Analysis

Histological analysis is based on the Gleason grading system. On the basis of architectural patterns, tumor cells are assigned a value between 1 and 5 with higher numbers assigned to cells that are more poorly differentiated and more aggressive. The Gleason score is the combination of the worst cell type plus the most predominant pattern. The score has significant prognostic information.

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Staging

Clinical staging for prostate cancer requires making an accurate assessment of the extent of disease spread (digital rectal examination, serum PSA, histological grade, and various imaging modalities). Table 1 compares the TNM versus the Whitmore-Jewett Staging system. These methods have been used to categorize patients based on their likelihood of disease spread prior to definitive therapy.

Management of Localized Disease

For the management of T1a disease there are data suggesting watchful waiting is as effective as a therapeutic intervention. For slightly more advanced disease there are three definitive management options of clinically localized prostate cancer (T1b, T2 and T3), which includes radical prostatectomy, radiation therapy (external beam radiation - EBRT or brachytherapy) and cryosurgical ablation. The 10-year survivals for radiation therapy (either EBRT or brachytherapy) and prostatectomy are quite comparable. Furthermore, a recent study found that there is no significant difference in the morbidity or mortality of radical surgery, EBRT or brachytherapy in patients with low risk of dying of prostate cancer defined as small volume disease, low or moderately differentiated tumors and low PSA.[2] Cryosurgical ablation of the prostate (CSAP) is considered investiga-

Table 1. Comparison of TNM staging and Whtmore-Jewett staging system

TNM Staging		Whitmore-Jewett Staging	
T0	Nonpalpable (focal or diffuse)	A1	Same as TNM
		A2	Same as TNM
T1a	Nonpalpable, with <5% of resected tissue with cancer, not high grade	B1	Palpable, < one lobe
T1b	Nonpalpable, with >5% of resected tissue with cancer and/or high grade		
T1c	Identified by needle biopsy because of PSA elevation		
T2a	Palpable, half of a lobe or less	B2	Palpable, one entire lobe
T2b	Palpable, >half of one lobe but not both lobes		
T2c	Palpable, involves both lobes		
T3a	Palpable, unilateral capsular penetration	C1	Palpable, outside capsule, not into seminal vesicles
T3b	Bilateral capsular penetration		
T3c	Tumor invades seminal vesicles		
T4	Tumor invades other structures (e.g., bladder neck, levator muscle, or external sphincter)	C2	Same as TNM
		D1	Pelvic lymph node or ureteral involvement
		D2	Disease outside abdomen (bone, distant lymph node, organ or soft tissue)

tional[3,4] and has not been compared in a large randomized study to other definitive treatments.

There is a data that adjuvant treatment with an LHRH agonist, starting simultaneously with external radiation, improves survival and local control in patients with locally advanced prostate cancer. Bolla and colleagues randomized 415 patients into external irradiation alone group or external irradiation plus goserelin.[5] Both groups received 50 Gy of radiation to the pelvis over a period of five weeks and additional 20 Gy over an additional two weeks as a prostatic boost. Patients in the combination treatment group received 3.6 mg of goserelin (Zoladex®) subcutaneously over four weeks starting on the first day of irradiation and continuing for 3 years. Five-year survival was significantly different between groups (79% in combination group vs 62% in radiotherapy group) as well as the proportion of surviving patients who were free of disease at five years (85% in combination group vs 48% in radiotherapy group).

Management of Advanced Disease

In the management of localized prostate cancer there is no clearly superior modality, yet there are a lot of different treatment options: single modality vs combined therapy, neoadjuvant vs adjuvant. However, medical treatment is uncontroversial in advanced prostate cancer. Nonetheless, no treatment options for metastatic disease has been shown to prolong survival, thus, one needs to encourage patients to participate in clinical trials in order to identify more active and effective regimens. In the rest of this review the new treatment options, as well as the investigational drugs that are under clinical evaluation will be discussed.

Hormonal Therapy

1. Androgen ablation

Prostate tumor growth is initially dependent on androgen-cell proliferation rate exceeds cell death rate. Furthermore, the majority of patients demonstrate a response with a reduction in circulating testosterone. This observation was initially made by Huggins and Hodges in the 1940s when they administered estrogen to patients with prostate cancer and showed a clinical benefit, they then readministered testosterone and demonstrated progression of the tumor.[6,7] Since then androgen ablation (hormone therapy) has been the cornerstone of initial therapy for the treatment of metastatic prostate cancer.

Testicular suppression is the mainstay of therapy in patients with advanced metastatic disease. This can be accomplished either by medical castration (LHRH agonist-depo leuprolide or goserlin, or more recently by LHRH antagonists that are under developed) or surgical castration. Medical castration was found to be equally

efficacious in controlling prostate cancer when compared with bilateral orchiectomy. The use of diethylstilbestrol (DES) for the initial treatment of prostate cancer has been abandoned because of the high incidence of vascular complications (i.e. approximately 3% of patients developed DVTs).

Because of increased screening few patients are diagnosed with metastatic disease. However, up to 50% of the patients that undergo a radical prostatectomy will have rising PSA within 10 years after the procedure. Thus, hormonal treatment will be required for these patients. The only question is when; when should androgen ablation therapy be instituted. The long-term side effects of continued testicular suppression are becoming more and more of a concern (decreased libido, osteoporosis, hot flashes, decreased muscular mass). The timing of hormonal ablation is being currently addressed in trials, however, there are efforts to develop more tolerable endocrine treatment options (discussed below).

a. Combined Androgen Blockade (CAB)

Significant resources have been devoted to determine if the addition of an androgen receptor antagonist (currently there are three such agents on the market-flutamide, bicalutamide, and nilutamide) prolongs the survival of patients with metastatic prostate cancer when combined with medical or surgical castration. The rationale for this combination is based on the fact that 10-30% of androgen comes from the adrenal glands, and orchiectomy or an LHRH agonist fails to inhibit these steroids. The most common toxicities associated with long-term CAB were decreased libido, impotence, decreased lean body mass, fatigue, gynecomastia and breast tenderness, anemia, diarrhea, changes in liver function tests, and nausea. Nonetheless, some 27 prospective randomized clinical trials have addressed this question. Twenty-four of the 27 found no significant difference in survival. Thus today, medical or surgical castration alone is considered standard of care for initial hormonal therapy in patients with metastatic disease or as adjuvant therapy.

b. Experimental approaches to androgen suppression

Newer approaches to hormonal therapy have focused on delaying the development of hormone resistance and to preserve the quality of life for the patient. One of the concepts is step-up therapy, where patients start antiandrogen in monotherapy and later with a rising PSA an LHRH agonist is added.

c. Intermittent therapy

A more common approach is intermittent hormonal therapy or intermittent androgen suppression (IAS) with an LHRH agonist. LHRH agonist are initiated for short period of time (approx. 6 months) then discontinued until there is evidence of a rise in PSA, then a second or subsequent course is administered. The rationale for IAS is 2-fold. First, as more men are screened and prostate cancer diagnosis and treatment occur earlier in the disease process, the potential effects of long-term hormonal therapy become considerable. Significant morbidity, such as impotence, hot flashes, osteoporosis, anemia, obesity, gynecomastia, and depression, is associated with androgen deprivation. IAS may reduce these undesirable side effects without sacrificing efficacy. Second, cyclical hormonal therapy may prolong the duration of hormone dependence of the cancer cells by allowing hormone-sensitive cells to repopulate the tumor between cycles of therapy.

The hope is that this approach could delay the occurrence of hormone resistance and preserve quality of life for the patients. However, this approach has not been compared to stand testicular suppression in a large randomized trial.

d. High-dose antiandrogen

High-dose bicalutamide (150 mg/day) as monotherapy is being developed as an initial treatment for metastatic hormone naive patients. Treatment with an antiandrogen (flutamide, bicalutamide, or nilutamide) as monotherapy may provide improved QOL over an LHRH agonist, particularly by allowing patients to maintain libido and sexual potency. It is expected that this regimen will gain FDA approval in 2001. Preliminary data suggest that it is equivalent to an LHRH agonist as an initial endocrine maneuver.

2. Secondary hormonal therapies

Therapeutic options for patients that are failing primary androgen ablation are limited. Patients are typically classified at this point as having androgen independent prostate cancer (AIPC) or hormone refractory disease (HRPC). Nonetheless, it is clear that if patients are receiving an antiandrogen, discontinuation is

recommend. Antiandrogen withdrawal has been associated with 20-30% of patients having a PSA decline (duration of response usually only 3 to 5 months). This response is usually limited to those that have received therapy for a prolonged period.

a. Glucocorticoids

Glucocorticoids (i.e. prednisone) clearly have some activity in patients with refractory disease. Sartor and colleagues found possible correlation between glucocorticoid dose and PSA decline.[8] Twenty-nine patients with AIPC received 10 mg of prednisone orally two times daily. Ten patients had ≥50% PSA decline and 4 patients had ≥ 75%. The mean PSA decline after initiating prednisone was 33%. The mean disease free survival was 2.8 months.

b. Megesterol

Megesterol acetate, a synthetic pro-gestin that inhibits luteinizing hormone release, as well as inhibits 5 alpha reductase, has been shown to have minimal activity in patient with progressive disease following androgen ablation. Based on its poor antiandrogen activity it should not be used in patients with AIPC. Nevertheless, megesterol is effective in suppressing hot flashes associated with primary testicular suppression.

c. Ketoconazole

Traditionally ketoconazole has been thought as being a secondary hormonal treatment. It has been known for years that ketoconazole can rapidly suppress testicular androgen. In fact it is commonly used to prevent flare associated with a LHRH agonist by administering ketoconazole for 2~3 days prior to the first injection in patients with newly diagnosed metastatic disease. Ketoconazole may also have direct cytotoxic effect on prostate cancer cells.[9] Ketoconazole as a single treatment (400 mg every 8 hours or 600 mg every 12 hours) was assessed for its efficacy in the management of hormonally pretreated patients with progressive metastatic prostate cancer.[10] The objective response was small and side effects and toxicity of the therapy were a major limitation of the treatment. The efficacy of ketoconazole (400 mg every 8 hours) in combination with hydrocortisone (20 mg each morning and 10 mg each evening) was evaluated in patients with AIPC.[11,12] Fifty-five to 62.5% of patients had a ≥50% decline in PSA and their median PSA response duration was 3.5 to 8.5 months. A phase II trial combining ketoconazole (1200 mg/d) with doxorubicin (20 mg/m^2 in a 24 h-infusion) was performed.[13] The combination treatment showed 55% PSA response rate (defined as ≥50% decline in PSA) PSA and 58% of patients with measurable soft tissue disease had a partial response.

Chemotherapy

The initial results of chemotherapy in the management of AIPC were quite disappointing. To date no chemotherapy regimen has been known to provide any survival benefit. However, with newer measures of response, including PSA changes and quality of life measures, aroused interest in chemotherapy. Anthracycline antibiotics, estramustine, taxanes, cyclophosphamide, platinums and etoposide may each have activity in AIPC and activity could be enhanced in combination regimen. Of the chemotherapy agents that have been studied, only mitoxantrone and estramustine are FDA approved for the management of prostate cancer metastases.

1. Estramustine combinations

Estramustine is a conjugate of a nitrogen mustard and estradiol. Its specific binding to microtubule-associated proteins and tubulin demonstrates antimitotic properties.[14] As a single agent the objective response of estramustine in phase II trials was low.[15] The rationale for combining estramustine with antimicrotubule agents was based on the hypothesis that greater cytotoxicity could be achieved using drugs that bind to different, but complementary protein targets in the microtubule. The combination of estramustine with antimitotic agent demonstrated promising results in several clinical trials.

a. Estramustine and taxanes

Clinical trial with paclitaxel as a single agent showed poor activity.[16] However, the response for the combination of taxane and estramustine was improved. The paclitaxel and estramustine combination showed PSA responses ranged between 53 and 65%,[17-20] and the responses for the combination of docetaxel and estramustine is 30~82%.[22-26] The measurable objective responses varied from 19% to 100%. Overall, the responses from the combination treatment are extremely promising.

b. Estramustine and vinca alkaloids

Estramustine and vinblastine are two microtubule

inhibitors which showed additive in vitro cytotoxicity. Several clinical trials evaluated estramustine/vinblastine combination in AIPC.[27-29] In 1992 Hudes and colleagues performed a phase II clinical trial enrolling 43 patients with AIPC and treated patients with oral estramustine 600 mg/m^2 on day 1 to 42 and vinblastine 4 mg/m^2 intravenously once a week for 6 weeks.[27] PSA response was observed in 61.1% and measurable response occurred in 30.5% of the patients. In a recent study, they compared vinblastine alone versus vinblastine plus estramustine utilizing the same dose in their previous study.[29] The estramustine and vinblastine combination was superior to vinblastine alone for ≥50% PSA decline. Interestingly, granulocytopenia was significantly lower for the combination compared with vinblastine alone. In another clinical trial 25 patients were treated with similar doses of combination and 54% of the patients showed PSA response.[28] The combination of estramustine and vinorelbine were also tested in a clinical trial.[30] Nine of 24 patients (37.5%) had a ≥65% decline in PSA levels with minimal toxicities.

c. Estramustine and etoposide

Estramustine and etoposide is another combination that showed in vitro cytotoxicity. Estramustine 15 mg/kg/d and etoposide 50 mg/m^2/d, were administered to 42 patients with AIPC.[31] Nine (50%) of 18 patients with soft tissue disease and 14 (58%) of 24 patients with disease limited to bone, demonstrated at least a 50% decrease in PSA. The same group conducted phase II trial (n=62) of estramustine and etoposide.[32] Twenty-four (39%) of 62 patients demonstrated a ≥50% decrease in PSA levels. Dimopoulos and colleagues reported that 56 patients treated with oral estramustine 140 mg three times a day and oral etoposide 50 mg/m^2/d for 21 days.[33] Thirty (58%) patients had a ≥50% PSA level decrease and median survival of all patients was 13 months.

d. Estramustine and anthracyclines

Culine and colleagues evaluated estramustine and doxorubicin in patients with AIPC.[34] Thirty-one patients were treated with a combination of daily oral estramustine (600 mg) and weekly intravenous doxorubicin (20 mg/m^2). Eighteen (58%) patients demonstrated a response with a 50% or more serum PSA decline and five (45%) of 11 patients with measurable disease achieved a partial response. Six patients were discontinued from the trial due to the occurrence of severe toxicity. Epirubicin, a anthracycline derivative of doxorubicin, was also tested in combination with estramustine in 24 patients with AIPC.[35] The biological response was similar (54%) to doxorubicin and estramustine combination but the toxicities were more tolerable with epirubicin plus estramustine.

e. Estramustine in combination with other agents

In a phase II trial estramustine (280 mg three times daily) and etoposide (100 mg/d for 7 days), with paclitaxel (135 mg/m^2 over 1 hour) were administered to 40 patients with AIPC.[36] Sixty-five percent of patients had a PSA response with a median duration of response of 3.2 months. Major toxicities were leukemia and anemia. Another phase II study evaluated estramustine, etoposide, and vinorelbine in 24 patients with AIPC.[37] Fifty-six percent of patients had a decline.

2. Mitoxantrone

Mitoxantrone is a synthetic anthracenedione derivative, which has shown antitumor activity against a wide range of cancer cells in vitro and in vivo. Mitoxantrone is structurally related doxorubicin. Earlier studies with mitoxantrone as a monotherapy showed only modest response assessed using National Prostatic Cancer Project (NPCP) criteria.[38-41] However, the occurrence of toxicities from mitoxantrone including nausea, vomitting, mucositis and cardiac toxicity was less than doxorubicin. Although no difference in overall survival was seen, statistically significant improvements in pain frequency and severity were experienced.

a. Mitoxantrone and steroid

A multicenter phase II trial of mitoxantrone (12 mg/m^2 iv q3wk) plus prednisone 10 mg daily was performed.[42] Twenty-five patients were enrolled and 30% of the patients showed 50% or more reduction in PSA levels. Myelosuppression was a primary toxicity, there was no serious nonhematologic toxicities.

In two larger multicenter randomized trials mitoxantrone plus steroids were compared with streroids alone. Tannock and colleague reported that 161 people were randomized to receive mitoxantrone 12 mg/m^2 intravenously every 3 weeks plus prednisone 10 mg/d or prednisone alone.[43] Thirty-three percent of patients in the combination group showed a 50% reduction in PSA levels while 22% of patients in the prednisone alone

group had the PSA response. They could not find any significant differences in PSA response between groups. However, palliative response (reduction in subjective pain or 50% reduction in analgesic usage) was found significantly different (P<0.0001), which had a response rate of 38% of the patients in the combination group versus 21% of the patients in prednisone alone group.

In the Cancer and Leukemia Group B (CALGB) study, larger number of patients (n=242) were randomized to mitoxantrone (14 mg/m^2) plus hydrocortisone (40 mg/d) group or hydrocortisone alone group.[44] The primary endpoint was survival, which showed no difference between groups (10.9 vs 11.8 months). Thirty-one percent of 119 patients who received both mitoxantrone and hydrocortisone had PSA decline of 50% or more and 17% of patients in a hydrocortisone alone group had the same response (P<0.05).

Although these studies demonstrate conflicting results in PSA decrease of 50% or more, mitoxantrone and prednisone combination treatment is a useful palliative therapy that provides improvements in pain and quality of life for about 40% with a tolerable toxicities. Following these reports mitoxantrone is approved by FDA for the treatment of metastatic prostate cancer pain control.

3. Cyclophosphamide

Cyclophosphamide, an alkylating agent, is one of the most extensively studied agents in the management of AIPC. Since most of the studies with cyclophosphamide did not use PSA as a response measurement, this agent is undergoing a new investigation using PSA decline as a measure of response. In an early study utilizing oral cyclophosphamide as a single agent, 6 of 30 patients (20%) showed objective partial responses with mild toxicities.[45] In another study, 54 patients with AIPC were treated with oral cyclophosphamide 100 mg/d for 20 days every 30 days and diethylstilbesterol 1 mg/d continuously.[46] Twenty of 54 patients (39%) demonstrated a greater than 50% decrease in PSA levels. Two of 6 patients (33%) with measurable soft tissue disease demonstrated partial responses.

Smith and colleagues treated 21 patients with intravenous high-dose cyclophosphamide (1.5 to 3 g/m^2 every 2 weeks) along with 5 mg/kg granulocyte-macrophage colony-stimulating factor (GM-CSF).[47] Seven of 21 patients (33%) demonstrated a decrease of greater than 50% in PSA. Toxicities were moderate, five patients required hospitalization for febrile neutropenia. Doxorubicin (40 mg/m^2) and cyclophosphamide (800~2,000 mg/m^2 in a dose-escalating schema) along with granulocytecolony stimulating factor (G-CSF) were evaluated in another clinical trial by Small and colleagues.[48] Sixteen of 35 patients (46%) had a greater than 50% decrease in PSA. Neutropenia was the most common side effects with 7.8% occurrence of febrile neutropenia. Small and colleagues tested the same combination of the drugs for the efficacy as second-line salvage chemotherapy in patients who progressed after the first-line treatment (suramin and hydrocortisone).[49] Three of 10 patients had a 75% or greater decline in PSA. Toxicity was moderate, neutropenia was most common without febrile neutropenia. Based on the activity and toxicity profile, cyclophosphamide should be considered as a treatment option for AIPC.

Investigational agents

Bisphosphonates

Bone is the most common site of metastases from the prostate cancer. Approximately 95% of metastatic carcinoma is osteoblastic metastases. Bisphosphonates are carbon-substituted pyrophosphate analogues, which are potent inhibitors of bone resorption. These compounds are indicated for Paget's disease and metastatic bone disease because of its activity on controlling osteolysis and reducing bone loss. Although the mechanism of action remains unknown, the inhibition of osteoclastic activity is recognized to be its major pharmacologic effects.

The efficacy of intravenous clodronate was shown in 56 patients with bone metastasis from prostate cancer.[50] Patients were randomly allocated to 2 cohorts and treated intravenously with either 300 mg clodronate or saline. Both pain score and analgesic consumption were very different between groups. On the other hand, oral clodronate appears to not be as effective as the intravenous formulation.[51]

The reports on clinical trials using etidronate are conflicting. Some of the studies found pain relief with the treatment of oral etidronate[52-54] while others could not find a differences.[55]

Several clinical trials reported favorable results with intravenous pamidronate.[56-58] Twenty-seven of 42 patients

were treated with intravenous pamidronate, 30 mg weekly for 4 weeks, then 30 mg every 2 weeks for 5 months in a controlled, nonblind trial.[56] Forty-four percent of treated patients showed an improvement in pain score during the study.

The effect of alendronate and paclitaxel on PC-3ML bone metastases in SCID mice was tested by Stearns and colleagues.[59] They found that alendronate pretreatment of mice (0.1 mg/kg/day, twice weekly or weekly) and dosing along with paclitaxel (10~50 mg/kg/day, twice weekly, or weekly) blocked the growth of PC-3ML tumors in the bone marrow and soft tissues in a statistically significant manner and improved survival rates significantly. A clinical trial utilizing ketoconazole and alendronate is currently being conducted at the National Cancer Institute in United States.

Angiogenesis inhibitors

In recent years one of the heavily investigated areas in cancer research is the inhibition of tumor angiogenesis. Tumor angiogenesis involves a complex multi-step cascade initiating with activation of endothelial cell proliferation, endothelial migration, and tube formation.60 Several agents, including SU6668, 2ME, suramin, CAI, thalidomide, endostatin, angiostatin, SU5416 and TNP 470 are in this category.

TNP-470 (AGM-1470)

TNP-470 is a semi-synthetic analogue of fumagillin, a natural product isolated from Aspergillus fumigatus, that inhibits angiogenesis in vitro.[61,62] In addition to its activity against endothelial cells this compound inhibits the tumor growth of hormone-independent prostate cancer PC-3 cells in a xenograft system.[62] It also inhibited the growth of the hormone-independent rat prostatic carcinoma cell line AT6.3.[61] Phase II clinical trials are currently in progress.

SU6668

SU6668 is a tyrosine kinase inhibitor that inhibited basic-FGF (bFGF)- and vascular endothelial growth factor (VFGF)-stimulated HUVEC proliferation.[63] SU6668 is currently completing phase I studies and will be examined in patients with AIPC.

cdk inhibitors

Cyclin dependent kinases are one of the enzyme related to progression of cell cycle. Flavopiridol is a synthetic flavone related to genistein, a novel antineoplastic agent isolated from soybean. Flavopiridol potently inhibits cell cycle progression in G1 or G2 phase and decrease proliferation of LNCaP cells in vitro and in a mouse xenograft model.[64] Drees and colleagues tested flavopiridol on 18 human tumor cell lines and 5 xenografts derived cell lines.[65] They concluded that flavopiridol demonstrated strong prostate-specific antitmor activity. A phase II clinical trial is currently being conducted in patients with AIPC.

Immunological treatment

Available treatments for metastatic prostate cancer have failed to demonstrate significant advances to date. Current efforts are now directed towards developments of novel strategies for the treatment of metastatic prostate cancer. Immunological treatment approaches for disseminated prostate cancer rely primarily on induction of tumor specific immune responses. So far, vaccines by which cytokine genes, e.g. IL-2 or granulocyte-macrophage colony stimulating factor (GM-CSF), are transfected into tumor cells to sensitize the host immune system by stimulating the expression of cell surface antigens have been disappointing. The autologous GM-CSF vaccine was prepared from removed tumor cells, transfected with the GM-CSF cytokine gene and then re-injected intradermally. A present objective response has not been seem. The in vivo allogeneic Allovax (G-vax) vaccine produced a positive PSA response in a few patients, but again objective clinical benefit has not been found.

Dendritic cells

Cancer cells can be irradiated and administered intradermally as vaccines. These engineered cells can secrete high levels of granulocyte-macrophage colony-stimulating factors (GM-CSF) by gene transfer in order to elicit an anticancer immune responses. Upon vaccination, dendritic cells process the phagocytosed antigen in cancer cells and present antigenic peptides to T cells. In a phase I trial of dentric cells, 8 patients with prostate cancer were enrolled and received vaccine treatment.[66] New antiprostate cancer cell antibodies were detected in serum samples from treated men after vaccination. Minimal toxicities were observed. Murphy and colleagues performed a phase II trials in patients with prostate cancer.[67] Thirty-seven patients received six infusion of dentric cells pulsed with prostate-specific membrane

antigen (PSMA) peptides at 6-week intervals. About 30% of the patients showed a positive response. Based on the data reported, dentric cell-based cancer vaccines appear promising.

Radiation Therapy

External beam radiation (EBR) is commonly utilized for the treatment of symptomatic bony lesions in patients with metastatic prostate cancer. It can either be administered to one lesion or to large regions of the body. Pain relief is relatively instant and dramatic. Greater than 50% of patients get significant control of their pain with EBR, however the side effects are an issue (neutropenia, thrombocytopenia, weakening of bone). Furthermore, repeat treatment to a particular region is prohibited.

Radioisotopes

Bone metastases is very common in prostate cancer. Several radioisotopes are known to help bone pain. Radioactive phosphorus (^{32}P) was the first agent approved by FDA for this indication. However, its high-energy beta emissions caused extensive myelosuppression and limited its use. There are 2 beta-emitting radioisotopes on the market, strontium-89 (^{89}Sr) and samarium-153 (^{153}Sm), have lower energy emission and can partially or completely decrease bone pain in up to 70% of patients. These agents work by localizing in the metabolically active bone surrounding osteoblastic lesions and delivering high-dose radiation therapy to those sites without affecting normal tissue. Both strontium-89 and samarium-153 received FDA approval for metastatic bone pain. The major toxicity of treatment is myelosuppression, especially thrombocytopenia. A randomized, phase III trial evaluated efficacy of strontium-89 in patients with AIPC.[68] One hundred patients received either strontium-89 as a single injection of 10.8 mCi or placebo. Strontium-89 was effective in reducing progression of disease as evidenced by new sites of pain and the requirement of further radiotherapy.

Conclusion

In conclusion, hormone manipulation, in particular androgen ablation via castration (medical or surgical), remains the cornerstone of therapy for hormone-sensitive metastatic prostate cancer. However, poor QOL and eventual progression to hormone-refractory disease remain major obstacles in the treatment of metastatic prostate cancer. Several new approaches to hormone manipulation are being studied to improve QOL and extend the duration of hormone-sensitivity. Intermittent therapy with an LHRH agonist may provide some improvements and stall the progression to AIPC. Antiandrogen monotherapy is another experimental approach that may provide improved QOL. Hormonal therapy for locally advanced prostate cancer is gaining evidence and support and may provide a survival benefit. Further studies are necessary to find improved therapies and treatment approaches.

Despite appropriate androgen ablation, all patients will inevitably progress to AIPC when androgen ablation therapy, though administered continuously as disease progresses, will no longer be effective in suppressing cancer growth. Antiandrogen withdrawal provides benefit to some patients with AIPC. The flutamide withdrawal response rate has been found to vary from 15% to 33% (as measured by a >50% decrease in PSA levels), and the response was found to last from 3.5 to 5 months. This endocrine withdrawal syndrome was originally observed in patients taking flutamide; however, objective improvement has since been observed following the discontinuation of bicalutamide, megestrol acetate, diethylstilbestrol, chlormadinone acetate, and cis-retinoic acid. Secondary hormonal manipulation may also provide some benefit to a small number of patients.

Due to prostate cancer screening the incidence of newly diagnosed metastatic prostate cancer has peaked and early detection and intervention may be playing a role in the decreased mortality rate associated with prostate cancer. The criteria for evaluation of the responses in case of hormone resistance are at last becoming better understood. This will allow objective and trustworthy comparisons between different treatments. The response from new combinations of chemotherapy is promising although there has been no survival benefit observed. New treatment modality, including angiogenesis inhibitors and gene therapy are currently under investigation.

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