



## 2nd Annual Multidisciplinary Prostate Cancer Symposium Late-Stage Prostate Cancer: The Emergence of Promising Interventions **CME**

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### Target Audience

This activity is intended for oncologists, urologists, radiologists, and surgeons interested in learning about advances in chemotherapy, the role of novel agents, and the niche for hormonal and bone-targeted therapies in the clinical setting of advanced prostate cancer.

### Goal

The objective of this activity is to highlight innovations in chemotherapy, hormonal therapy, and bone-specific therapy; and provide a venue for a key opinion leader to postulate the benefit of these novel approaches for the Oncology, Urology, Radiology, and Surgery audiences on Medscape.

### Overall Learning Objectives

Upon completion of this activity, participants will be able to:

1. Describe advances in surgery, radiation therapy, chemotherapy, novel and hormonal agents, and immunotherapy for treating prostate cancer.
2. Review the imaging modalities used to evaluate prostate cancer.
3. Detail the relationship between molecular pathways and targeted molecular therapies in the treatment of prostate cancer.

### Learning Objectives for this CME Activity

Upon completion of this activity, participants will be able to:

1. Detail the role of novel chemotherapeutic agents in the setting of advanced prostate cancer.
2. Describe new hormonal and bone-targeted agents used in the setting of advanced prostate cancer.
3. Discuss the value of emerging chemotherapeutic protocols to treat advanced prostate cancer.

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## Chemotherapy and Novel Agents for Patients With Advanced Prostate Cancer: New Developments

Robert Dreicer, MD, FACP

### Introduction

The demonstration in 2 randomized trials that a modest but real survival benefit can be derived from docetaxel-based chemotherapy (when compared with the benefit seen in patients receiving mitoxantrone and prednisone) has forced physicians to reevaluate the management of patients with advanced prostate cancer.<sup>[1,2]</sup> While docetaxel-based chemotherapy is an important first step toward increased survival, androgen-resistant, metastatic prostate cancer remains an incurable disease. Many challenges remain, including the optimal timing and duration of therapy and options for patients whose disease progresses following docetaxel-based therapies. Significant efforts are under way to augment the activity of taxane-based therapies and to evaluate novel agents in various settings of advanced disease.

Presented here is an overview of a series of abstracts addressing refinements in the use of chemotherapy in advanced disease and early results using novel agents presented at the 2006 Prostate Cancer Symposium in San Francisco.

### Chemohormonal Therapy

Over the years, investigators have been intrigued by the possibility of augmenting the response to chemotherapy by integrating hormonal therapy cycling into a novel treatment paradigm. Rathkopf and colleagues<sup>[3]</sup> conducted a phase 2 trial of docetaxel in combination with rapid hormonal therapy cycling in 60 patients with noncastrate metastatic prostate cancer. Patients with evidence of progressive prostate-specific antigen (PSA) values with or without radiographic evidence of metastatic disease and noncastrate levels of testosterone received six 28-day cycles of leuprolide (7.5 mg intramuscularly) and docetaxel 75 mg/m<sup>2</sup> on day 1, followed by topical testosterone repletion on days 22 through 28. The primary endpoint was the proportion of patients at 6 and 18 months who achieved PSA values 0.05, 0.5, or 2.0 ng/mL or less following surgery or radiotherapy, or who had untreated metastatic disease, respectively. Nine of 25 (36%) patients with increasing PSA and 13 of 37 (35%) patients with noncastrate metastatic disease achieved the primary end point at 6 months. Therapy was relatively well-tolerated, although grade 3 and 4 neutropenia occurred in 61% of patients, and 10% of patients had febrile neutropenia. The authors speculate that the increased incidence of neutropenia may be related to decreased clearance of docetaxel in the setting of noncastrate levels of testosterone.

### Intermittent Chemotherapy Administration

In an effort to gain further insight into the role of "intermittent" chemotherapy -- that is, re-treatment of patients with taxane-based therapy after a clinical response is achieved and treatment is discontinued -- Beer and colleagues<sup>[4]</sup> presented data collected prospectively from the ASCENT study in which docetaxel (36 mg/m<sup>2</sup>) was administered weekly 3 out of 4 weeks with or without calcitriol (DN-101) for 10 to 12 cycles. Patients enrolled in the ASCENT study could suspend treatment if they had a confirmed reduction in serum PSA of 50% or more and a serum PSA 4 ng/mL or less. Patients underwent planned serial imaging and PSA monitoring, and therapy was resumed when serum PSA levels rose by 50% or more and was greater than 2 ng/mL or for any other evidence of disease progression. Of the 250 patients enrolled in the study, 18% received intermittent therapy (DN-101 + docetaxel 20%, docetaxel alone

16%). The median duration of the first chemotherapy holiday was 16 weeks. On resumption of treatment after the first chemotherapy holiday, 50% of patients had a reduction in serum PSA levels of 50% or more, with 35% meeting criteria for stable PSA and 15% progression.<sup>[5]</sup> This experience suggests that a subset of patients undergoing chemotherapy with docetaxel can be given a holiday from therapy with the expectation of a response when therapy is restarted. The impact of this intermittent strategy on patient survival and overall quality of life remains undefined.

## Second-Line Chemotherapy for Androgen-Resistant Metastatic Prostate Cancer

A modest survival benefit from docetaxel-based chemotherapy has recently been shown.<sup>[1,2]</sup> As a result, investigators around the world are actively studying therapeutic options for second-line therapies.

Saad and coworkers<sup>[6]</sup> evaluated the utility of docetaxel and prednisone in patients with androgen-resistant metastatic disease with evidence of progression following chemotherapy with mitoxantrone and prednisone. In an interim report of this ongoing study, 30 patients with disease progression following standard mitoxantrone and prednisone received docetaxel 75 mg/m<sup>2</sup> every 3 weeks with prednisone 5 mg twice a day. At study entry, 80% had bone pain and a median PSA of 112 ng/mL. At the time of this report, PSA reductions greater than 50% were seen in 70% of patients, and a 57% decline in analgesic scores indicated some degree of pain improvement in 80% of patients. Two patients had experienced febrile neutropenia. Progression-free survival is currently 7 months, and median survival has not yet been determined.

Ohlmann and colleagues<sup>[7]</sup> evaluated 25 patients with androgen-resistant metastatic prostate cancer with PSA progression following docetaxel-based chemotherapy. Progression was defined as continuous increase in PSA level measured at 3 consecutive time points 2 weeks apart and a level higher than 2 x nadir after the first 12-week cycle of chemotherapy. A PSA response was seen in 18 of 25 (72%) of patients, and the mean duration of response was 5.8 months. Five and 3 patients, respectively, experienced grade 3 to 4 anemia and leukopenia. Grade 3 to 4 nonhematologic toxicities included nail bed changes in 20%, diarrhea in 12%, and fluid retention in 12%.

Rosenberg and colleagues<sup>[8]</sup> performed a randomized phase 2 trial of ixabepilone, a novel epothilone, compared with mitoxantrone and prednisone in patients with disease progression during or within 60 days of stopping docetaxel chemotherapy. Patients were randomized to either mitoxantrone 14 mg/m<sup>2</sup> administered every 3 weeks with daily prednisone 5 mg twice daily or ixabepilone 35 mg/m<sup>2</sup> given every 3 weeks. Crossover at time of progression was permitted. The study accrued 41 evaluable patients in each arm. With a median follow-up of 5 months, confirmed posttherapy PSA decreases of 50% or more were observed in 17% of the patients receiving ixabepilone and in 20% of those receiving mitoxantrone and prednisone. Median survival from protocol entry was 12.5 months for ixabepilone and 13 months for mitoxantrone. Hematologic toxicity included grade 3 and 4 neutropenia in 41% of patients receiving ixabepilone and in 54% of patients treated with mitoxantrone. One patient treated with ixabepilone died of a therapy-related complication. The authors concluded that both agents have only modest activity in this setting with acceptable toxicity profiles.

## Novel Agents

FK 228 is a bicyclic depsipeptide that inhibits histone deacetylase. Such inhibition can result in G1/G2/M arrest, differentiation, and apoptosis. Molife and colleagues<sup>[9]</sup> presented early results from an ongoing phase 2 trial of FK 228 administered intravenously at 13 mg/m<sup>2</sup> on days 1, 8, and 15 of a 4-week cycle for up to 6 cycles. Eligible patients had castrate metastatic prostate cancer and were chemotherapy-naïve. Of the 16 patients included in this interim report, 12 were evaluable for radiologic response. One patient achieved a confirmed radiographic partial response, and 4 others had stable PSA values on treatment. The most common adverse events were grade 1 and 2 fatigue, nausea, and vomiting.

Lin and coworkers<sup>[10]</sup> reported a phase 2 trial of ketoconazole and granulocyte-macrophage colony stimulating factor (GM-CSF). Eligible patients had progressive castrate metastatic prostate cancer and were immunotherapy-naïve. Ketoconazole 400 mg was given 3 times daily with hydrocortisone at replacement doses. GM-CSF at 250 mcg/m<sup>2</sup> was administered subcutaneously on days 15 through 28 of each 28-day cycle. The study was powered to detect a 50% prolongation of the median response duration relative to historical controls (5 to 7.5 months). At the time of this interim report, 42 of the planned 48 patients had been enrolled (30 with metastatic disease and 12 with PSA evidence of disease only). The 35 patients evaluable for response were treated for a median of 5.1 months. Twenty-four (69%) have experienced a reduction in serum PSA of 50% or more associated with stable scans. Sixteen of 30 patients with metastatic disease and 8 of the 12 patients with only PSA progression have also had a reduction in serum PSA of 50% or greater. Therapy was very well-tolerated; the most common adverse events were grade 1 injection site

reactions and fatigue. Accrual and follow-up for this study are ongoing.

A report by Wu and colleagues<sup>[11]</sup> of the National Cancer Institute reminds us that relying on PSA response alone may be misleading in the assessment of novel agents. These researchers conducted a phase 2 trial of sorafenib, a potent inhibitor of Raf-1 and multiple receptor kinases involved in tumor progression, that was recently approved by the FDA for advanced kidney cancer. Twenty-two patients with androgen-resistant metastatic prostate cancer were treated twice daily with 400 mg of sorafenib. The primary end point of this study was a 50% progression-free interval at 4 months. Nineteen of 22 patients had evidence of disease progression, with 10 on the basis of PSA criteria alone. Of interest, 5 of the patients with PSA progression alone were noted to have decreased PSA levels after discontinuing therapy. Two patients with disappearance of metastatic bone disease on serial bone scan assessment had concomitant PSA progression.

## Conclusions

Although the data presented at the 2006 ASCO prostate meeting will not necessarily change clinical practice standards, a growing body of evidence suggests that there is a subgroup of patients with advanced prostate cancer previously treated with docetaxel who will respond to reintroduction of this agent. This observation will need to be confirmed but will probably have clinical relevance given the current lack of a standard, effective, second-line therapy and the likelihood that patients will increasingly receive docetaxel-based therapy earlier in the disease course. Three upcoming studies involving docetaxel will be exploring chemotherapy in the following settings: 1) neoadjuvant (CALGB-90203, which will involve neoadjuvant docetaxel followed by radical prostatectomy vs prostatectomy), 2) adjuvant (a 3-arm study evaluating chemotherapy vs hormonal therapy vs treatment at progression), and 3) metastatic (ECOG "CHARTED"-untreated patients with metastatic disease randomized to receive standard androgen deprivation therapy with or without 6 cycles of docetaxel-based therapy).

Several novel agents have interesting early activity in advanced disease, and we are again reminded that understanding how these agents work at the molecular level will be increasingly important to avoid abandoning active agents because they alter PSA expression in the wrong direction while having direct antitumor effects.

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## Hormonal and Bone-Targeted Therapies for Patients With Advanced Prostate Cancer: Recent Advances

Robert Dreicer, MD, FACP

### Introduction

It has been more than 6 decades since androgen-deprivation therapy (ADT) was first shown to be effective in management of advanced prostate cancer. During the past 15 years, there have been major refinements in the clinical application of hormonal therapy, which in combination with the widespread measurement of prostate-specific antigen (PSA) levels in serum, has dramatically increased both the number of patients treated and the length of time that they receive hormonal therapy.

One of the characteristic features of advanced prostate cancer is the high incidence of metastatic bone disease. The past decade has seen an increased focus in both basic and clinical investigation of the biology and clinical management of this debilitating disease.

This brief overview will discuss a series of abstracts dealing with various aspects of ADT and bone-targeted approaches presented at the 2006 Prostate Cancer Symposium held in San Francisco.

### Hormonal Therapy

The early prostate cancer (EPC) program<sup>[1]</sup> comprises 3 randomized, double-blind, placebo-controlled trials designed for combined analysis. These trials investigated the addition of bicalutamide 150 mg to standard care (radical prostatectomy, radiotherapy, or watchful waiting). See and colleagues<sup>[2]</sup> presented findings from the EPC program's third analysis of data, which had a median follow-up for the radiotherapy-treated subgroup. In this subgroup, 699 men received bicalutamide 150 mg and 671 received placebo. In a subset of patients with locally advanced disease ( $n = 305$ ), bicalutamide 150 mg adjuvant to radiotherapy significantly improved objective progression-free survival (hazard ratio, 0.56;  $P < .001$ ) and overall survival (hazard ratio, 0.65;  $P = .03$ ) compared with placebo. There were no significant differences seen in either of these end points in patients with localized disease. The authors noted that this study was the first to show a significant overall survival benefit in patients with locally advanced disease treated with any noncastration-based hormonal adjuvant therapy. However, Dr. Mario Eisenberger of Johns Hopkins cautioned against overinterpretation of the results from this very small subset of patients.

Bianco and coworkers<sup>[3]</sup> analyzed a large consecutive cohort of patients with rising PSA levels following radical prostatectomy. Their goal was to better define a tool to predict the utility of ADT. The study group was drawn from a cohort of 4500 men who underwent radical prostatectomy for clinically localized disease, of which 693 subsequently had evidence of increasing PSA. Of the 693 men, 355 received ADT and were followed prospectively for a median of 12 years from the time of radical prostatectomy and a median of 5.3 years following initiation of hormonal therapy. During this time, 93 men developed evidence of metastatic prostate cancer and 36 died from causes unrelated to prostate cancer with an undetectable PSA. The median response time to ADT until development of metastatic disease was 12.4 years. Within 8 months of ADT, PSA nadir was less than 0.2 in 285 (80%) of the men. The median time to metastatic disease for those who did not reach an undetectable PSA level was 35 months. The authors concluded that many men treated for a rising PSA after radical prostatectomy have a prolonged duration of response to ADT and that they have developed a model that can identify patients with a shorter-term response to this approach who would be candidates for additional interventions.

Shiple and colleagues<sup>[4]</sup> examined the question of the optimal timing of ADT in patients with PSA progression following radiotherapy by performing a secondary analysis of data from the RTOG 86-10 trial.<sup>[5]</sup> This trial randomized 471 patients with bulky-stage T2 to T4 disease to receive either 70-Gy radiotherapy alone or combined with neoadjuvant and concomitant ADT. It demonstrated that patients with prostate carcinoma of 2 to 6 on the Gleason scale showed a highly significant improvement in local control, reduction in disease progression, and overall survival after a short course of androgen ablation administered before and during radiotherapy. In the secondary analysis, 247 (54%) patients have received subsequent salvage hormonal therapy. Median follow-up was 9 years, and patients were followed for a median of 5.5 years following initiation of ADT. For patients with metastatic disease present at the start of ADT, overall survival and disease-specific survival were significantly reduced when compared with those without metastases at the start of ADT ( $P < .001$ ). An important limitation of this retrospective study is that it did not evaluate PSA doubling time, which may better predict long-term survival than absolute PSA.

### Impact of Androgen-Deprivation Therapy on Bone

Saad and colleagues<sup>[6]</sup> performed a retrospective analysis on the patients in their prospective, placebo-controlled, randomized trial of zoledronic acid.<sup>[7]</sup> Using a Cox regression model, they assessed the correlation between fractures or bone markers (urinary N-telopeptide and bone alkaline phosphatase) and death or skeletal events, adjusting for treatment group. They found that patients who had a fracture while they were in the study had a shorter survival time than those who did not, and that patients with high urinary N-telopeptide levels seemed to have a significantly increased risk for skeletal events.

Three other abstracts provided additional insight into the potential role of bisphosphonates in patients receiving ADT. Casey and colleagues<sup>[8]</sup> conducted an open-label, placebo-controlled, multicenter study to determine whether treatment with zoledronic acid can prevent bone loss in patients undergoing ADT with goserelin acetate. Two hundred men with locally advanced prostate cancer were randomized in a 1:1 ratio to receive goserelin acetate with or without zoledronic acid 4 mg every 3 months for a year. The primary end point was the percentage change from baseline in bone mineral density of the femoral neck and hip, changes in height, and interval development of metastatic disease. Interim results at 1 year are available on 80 patients and show decreased bone mineral density at all measured sites in patients receiving goserelin alone. Overall, patients treated with zoledronic acid in addition to goserelin experienced improvement in bone mineral density up to 4% compared with up to 2% in men treated with goserelin alone.

Nelson and colleagues<sup>[9]</sup> enrolled 112 men with nonmetastatic prostate cancer who were on ADT for at least 6 months in a 2-year, randomized, double-blind, placebo-controlled study of oral alendronate 70 mg once weekly. All patients received calcium and vitamin D supplementation. In this interim report at 1 year of follow-up, only 9% of men had normal bone mass at baseline, 39% had osteoporosis, and 52% had low bone mass. In men treated with alendronate, bone mass increased significantly ( $P < .05$ ) after 12 months at the spine and hip compared with significant loss in those locations in men in the placebo group. Therapy was well-tolerated; no differences in adverse events were noted between the 2 groups.

Ryan and colleagues<sup>[10]</sup> evaluated the role of bisphosphonates initiated later in the course of ADT. One hundred-twenty men without metastatic bone disease who had received ADT for fewer than 12 months were randomized to receive either zoledronic acid 4 mg administered intravenously every 3 months or placebo. Patients were stratified according to duration of ADT. The primary end point was bone mineral density in the femoral neck and lumbar spine at 6 and 12 months. Patients in the placebo group lost more than 2% of bone mineral density at both measured sites over the 12-month study period. Compared with placebo, therapy with zoledronic acid increased bone mineral density at both sites by 3.6% and 6.7%, respectively ( $P = .0004$  and  $P < .0001$ ), per year. The effects of zoledronic acid on bone mineral density were not differentiated by the duration of ADT. The authors concluded that their findings support current guidelines that recommend initial monitoring of bone mineral density with delayed initiation of bisphosphonates until evidence of bone mineral density loss appears.

An important clinical question regarding the role of bisphosphonates is their utility in patients who have already had a skeletal event while receiving hormonal therapy. Saad and coworkers<sup>[11]</sup> conducted a series of retrospective analyses on selected cohorts of patients enrolled in their prospective, placebo-controlled, randomized trial of zoledronic acid. Data for this analysis were analyzed from a 15-month core study and a 9-month extension study. End points included the percentage of patients with a first or second in-study skeletal event and mean annual incidence of skeletal events. The investigators found that among patients who had experienced a skeletal event before study entry, fewer patients in the zoledronic acid arm had 1 or more skeletal events during the entire study (24 months) than those in the placebo arm (41% vs 51%;  $P = .215$ ). After 15 months of therapy, zoledronic acid significantly reduced the percentage of patients who had a second in-study skeletal event (21% vs 31%;  $P = .017$ ) and reduced the mean

annual incidence of skeletal events. The authors concluded that zoledronic acid appears to provide ongoing benefits to men with prostate cancer and bone metastases even after they have a skeletal event. This observation is clearly of interest but will require prospective validation because of the implications for both therapy-related toxicity and costs.

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## Balancing Interventions With Quality of Life in Advanced Prostate Cancer

Hossein Jadvar, MD, PhD

Prostate cancer is the most common type of cancer affecting men in the United States. In 2003, the estimated incidence of and deaths from this disease were 220,900 and 28,900, respectively.<sup>[1]</sup> In this report, we summarize selected data related to the treatment of locally advanced, recurrent, and metastatic disease that were presented at the 2nd Annual Meeting of the Multidisciplinary Prostate Cancer Symposium held in San Francisco, California, February 24-26, 2006. The meeting was cosponsored by the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Prostate Cancer Foundation (PCF), and the Society of Urologic Oncology (SUO).

Androgen-independent metastatic prostate cancer is incurable. However, a host of new treatments have entered

clinical trials that are designed to improve clinical outcomes while safeguarding quality of life for patients with this disease.

## Aspects of Docetaxel Therapy

The findings of several ongoing studies of docetaxel-based chemotherapy were presented. This therapy has been shown to confer a significant survival benefit in this clinical setting. Unfortunately, about 80% of men with androgen-independent metastatic disease have PSA relapse within 12 months; median time to progression is about 6 months after the initial response to docetaxel. In 1 investigation, 25 patients with PSA relapse after docetaxel-based chemotherapy received repeated treatment with low-dose docetaxel; the primary endpoint was a decline greater than 50% in PSA levels.<sup>[1]</sup> A PSA response was noted in 72% of patients, with a mean duration of response of 5.8 (range, 3 to 10) months. These findings suggested that rechallenge with low-dose intermittent docetaxel may be a well-tolerated, effective treatment option in men with hormone-refractory disease and PSA progression following initial response to docetaxel-based chemotherapy.

Another study combined standard docetaxel-based chemotherapy with capecitabine in a phase 2 clinical trial.<sup>[2]</sup> The results of the first stage of this trial have suggested that capecitabine combined with docetaxel is efficacious, showing a 67% partial remission rate and a decline in PSA level of at least 50%. Another randomized phase 2 trial showed that the combination of docetaxel and estramustine has significant therapeutic efficacy in men with hormone-refractory disease.<sup>[3]</sup> Similar favorable results were reported by G. Gravis MD, and coworkers, who showed that docetaxel combined with estramustine on a weekly basis can achieve a clinical benefit response of 33%, has a median response duration of 74 days, and is associated with a PSA response of 53%.<sup>[4]</sup>

S. Tomek, MD, and colleagues reported the findings of a phase 2 clinical trial on the use of weekly docetaxel vs weekly vinorelbine as first-line chemotherapy in patients with androgen-independent metastatic prostate cancer.<sup>[5]</sup> The authors concluded that weekly docetaxel was more efficacious than vinorelbine in terms of 50% PSA decline (62.5% vs 11.1%, respectively), while the overall toxicity profile of both regimens was mild. The results of a phase 2 clinical trial of combined diethylstilbestrol (DES) and docetaxel were reported by B. Montgomery, MD, and coworkers.<sup>[6]</sup> This trial included 26 men with metastatic hormone-refractory disease, and response was assessed by RECIST criteria and by PSA decline greater than 50% maintained over 4 weeks. To date, the median number of treatment cycles has been 6, with a median follow-up after chemotherapy of 6 months (range, 1 to 18 months). The overall response rate for 23 patients was 74%. Six patients had toxicity greater than grade 3, 1 died of unrelated causes, and 1 died due to steroid-induced ulcer complications. The authors of this paper concluded that DES improves the therapeutic index of docetaxel and should be considered as part of a combination regimen for future trials.

The combination of docetaxel and gefitinib was assessed by a group from Switzerland.<sup>[7]</sup> This phase 2 trial enrolled 37 chemotherapy-naive patients who received the combined treatment. Gefitinib was given continuously while docetaxel was limited to up to 6 cycles. PSA response (defined as at least a 50% decline in PSA) was 43.2% at 2 months and 45.9% at 4 to 6 months. Median duration of PSA response was 215 days, median time to PSA or radiologic progression was 165 days, and median survival was 447 days. About 38% of patients discontinued combination therapy due to significant adverse events.

The initial results of the multicenter ASCENT trial were reported by T. Beer, MD, and colleagues.<sup>[8]</sup> ASCENT was a multi-institution, randomized, clinical trial designed to compare the effectiveness and safety of weekly DN-101 plus docetaxel to placebo plus docetaxel in patients with chemotherapy-naive metastatic androgen-independent prostate cancer. Patients were allowed to suspend treatment if they had a confirmed decrease in PSA exceeding 50% and a PSA level 4 ng/mL or less. PSA was monitored every 4 weeks. Treatment was resumed when PSA increased more than 50% and was 2 ng/mL or higher. The study concluded that this strategy results in clinically meaningful chemotherapy holidays and can be offered to about one fifth of men who, when treatment is restarted, will again respond (85%, as evaluated by stable or declining PSA levels).

## Hormonal Therapies Show Promise

The role of adjuvant androgen-deprivation therapy (ADT) in surgically treated men with prostate cancer invading the seminal vesicles was discussed by B. Inman, MD, and coworkers from the Mayo Clinic.<sup>[9]</sup> Men who received immediate postoperative ADT had considerably better outcomes than those who did not receive ADT (10-year biochemical-free survival, 60% vs 23%; 10-year cancer-specific survival, 97% vs 90%). These findings suggested that immediate adjuvant ADT should be strongly considered in men with prostate cancer invading the seminal vesicles.

A group of Belgian and Danish researchers evaluated the use of degarelix (a gonadotrophin-releasing hormone-receptor blocker) in 187 men with prostate cancer (19% metastatic, 32% locally advanced, 22% localized, and 27% M0/MX and not T-staged).<sup>[10]</sup> Degarelix therapy for 1 year resulted in rapid, sustained suppression of testosterone and PSA decline without untoward complications.

The efficacy of atrasentan therapy was also evaluated by M. Carducci, MD, and colleagues.<sup>[11]</sup> Patients underwent a randomized, double-blind, placebo-controlled multinational trial of atrasentan. Disease progression was defined as radiographically identified new lesions, or by clinical criteria (eg, pain requiring significant opioids). This study showed that, in men with hormone-refractory osseous metastatic disease, the administration of atrasentan can forestall disease progression.

The results of a phase 2 trial of low-dose (LD, 1.25 mg once daily) and high-dose (HD, 1.25 mg three times daily) conjugated estrogens was reported by W. Oh, MD, and coworkers from Harvard Medical School.<sup>[12]</sup> Patients were encouraged to receive prophylactic breast irradiation, and warfarin anticoagulation was also given unless it was contraindicated. HD estrogen therapy was associated with a 32% response rate, while no response was observed in the LD group. The median time to progression was 3.2 to 3.3 months for both regimens. Toxicity was modest, although thromboembolism was seen despite prophylactic anticoagulation with warfarin.

Stanford researchers examined the potential synergistic effect of calcitriol and naproxen in men with recurrent prostate cancer.<sup>[13]</sup> The underlying physiologic basis for this investigation was that calcitriol and nonsteroidal antiinflammatory drugs (such as naproxen) exert antiproliferative effects by decreasing prostaglandins. The early results of this study demonstrated that the combination of calcitriol (0.5 mcg/kg per week) and naproxen (400 mg twice daily) may be an effective therapy for prostate cancer recurrence after primary therapy. Additional studies, which are under way, are necessary to confirm and support these early encouraging findings.

### **Postradiation Salvage Surgery: Dealing With Bone Pain and Posttherapy PSA Spikes**

Salvage prostatectomy in men with locally recurrent prostate cancer after definitive radiation therapy is a challenging course of action. C. Ohlmann, MD, and colleagues performed salvage prostatectomy in 21 men with radio recurrent prostate cancer and no evidence of metastatic disease.<sup>[14]</sup> These researchers concluded that, in this subset of patients, salvage prostatectomy is a technically challenging but feasible approach when used in selected patients. However, as the researchers noted, patient follow-up was too short to evaluate outcomes with a high degree of accuracy. More extensive information on outcomes would be helpful in deciding whether salvage prostatectomy is a viable option in selected patients.

Control of bone pain is important in men with osseous metastatic prostate cancer. O. Sartor, MD, reported the findings of a multicenter trial designed to examine the safety and efficacy of single and repeated dosing of Sm-153 leixidronam (Sm-153).<sup>[15]</sup> Sm-153 (1.0 mCi/kg) was given to 157 patients for treatment of bone pain. There were 48 patients given repeated dosing. Adverse events were assessed at baseline, weeks 1 to 6, and 8 weeks after dosing. Repeated dosing was offered to men who had an initial palliative response and recovery of leukocyte and platelet counts. The median interval between first and second treatments was 137 days and 78 days after the second infusion. The authors of this study concluded that repeated dosing of Sm-153 is well-tolerated and is a reasonable palliative option in the appropriate clinical setting. The same investigators analyzed a series of variables that may predict a palliative response in patients receiving Sm-153 for painful osseous metastases.<sup>[16]</sup> They found no particular clinical variables that could predict the success of palliative response to Sm-153. This suggests that the variables that contribute to response may be multifactorial, complex, and at least partially related to difficult-to-measure considerations, such as the patient's tolerance of pain and subjective pain assessment.

The outcome of men with rapidly rising PSA after definitive local therapy was investigated by a multicenter team led by N. Rodrigues, MD.<sup>[17]</sup> The study population included 67 men with PSA doubling time 6 months or less after radical prostatectomy or external-beam radiation therapy for localized prostate cancer. Men were followed for 2.9 years beginning 8 months after ADT initiation. A PSA nadir greater than 0.2 ng/mL and a Gleason score of 8 or higher were significantly associated with short time to prostate cancer-specific mortality (PCSM). The study concluded that men with PSA doubling time 6 months or less and at high risk for PCSM would be candidates for phase 3 chemotherapy clinical trials. In another study, it was determined that pretreatment PSA doubling time may be a useful predictor of response to chemotherapy in men with androgen-sensitive PSA progression after local therapy.<sup>[18]</sup> In this study, a PSA doubling time of 70 days was associated with a sensitivity of 70% and specificity of 71%.

In summary, all phases of clinical trials are being conducted to address the difficult problem of treating men with

hormone-refractory disease. The general goals of these studies are to find ways to increase survival while maintaining a reasonable quality of life and minimizing toxicity and complications.

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## Authors and Disclosures

### Author

#### **Hossein Jadvar, MD, PhD**

Assistant Professor of Radiology and Biomedical Engineering, Keck School of Medicine, University of Southern California, Los Angeles

Disclosure: Hossein Jadvar, MD, PhD, MPH, has disclosed no relevant financial relationships.

#### **Robert Dreicer, MD, FACP**

Professor of Medicine; Chairman, Department of Solid Tumor Oncology, Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio

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### Editor

#### **Margie Miller**

Program Director, Hematology-Oncology

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