A Wealth of New Options: A Case Presentation of the Management of Castration-Recurrent Prostate Cancer

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Seminars in Oncology

At times we encounter clinical problems for which there are no directly applicable evidence-based solutions, but we are compelled by circumstances to act. When doing so we rely on related evidence, general principles of best medical practice, and our experience. Each "Current Clinical Practice" feature article in *Seminars in Oncology* describes such a challenging presentation and offers treatment approaches from selected specialists. We invite readers' comments and questions, which, with your approval, will be published in subsequent issues of the Journal. It is hoped that sharing our views and experiences will better inform our management decisions when we next encounter similar challenging patients. Please send your comments on the articles, your challenging cases, and your treatment successes to me at Dr.gjmorris@gmail.com. I look forward to a lively discussion.

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Current Clinical Practice Feature Editor

Adenocarcinoma of the prostate is the most common malignant disease affecting men in the world. Many advances in treatment have been made over the years, which have greatly altered the natural history of the disease. Making great strides from the first prostatectomies performed in the early 1900s and the use of "chemical castration" with estrogen supplements in the 1940s, and later luteinizing hormone–releasing hormone (LHRH) agonists, the recent progress has been impressive. Surgical and radiation techniques currently used have augmented precision with the use of robotic prostatectomies and intensity-modulated radiation therapy, respectively. Similarly, medical treatments such as new hormonal agents and chemotherapy have improved both quality of life and mortality in patients with early-stage and advanced cancers.

The approach to metastatic disease most commonly starts with androgen-deprivation therapy (ADT) using LHRH agonists, either alone or in combination with an anti-androgen such as bicalutamide. Inevitably, however, many patients will eventually have biochemical and/or visceral progression of disease. For patients with castrate-recurrent prostate cancer (CRPC), novel treatments are now available. In those patients with asymptomatic CRPC without evidence of visceral disease, the immunotherapy sipuleucel-T was approved in April 2010. The Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial, a multicenter phase III randomized controlled trial, showed a survival advantage—25.8 months compared to 21.7 months in the control arm—with sipuleucel-T despite the lack of biochemical improvement or decrease in bone lesions seen on imaging.[1] On the other hand, for CRPC patients with symptomatic disease or those with visceral progression, docetaxel administered every 3 weeks is the standard of care. Docetaxel, in combination with prednisone, has been shown to modestly prolong survival when compared with the previous standard of mitoxatrone plus prednisone.[2–4] Regarding second-line therapy in metastatic disease, another taxane, cabazitaxel, was approved for use in June 2010. The TROPIC trial demonstrated a 2.4-month improvement in overall survival compared with mitoxantrone among patients already treated a docetaxel.[5,6] Most recently, in April 2011, abiraterone was approved for use in this patient subset. A phase III study showed that abiraterone extended median survival by 14.8 months versus 10.9 months in the control arm receiving corticosteroids alone.[7] These new therapeutic options raise new questions regarding the optimal timing and use of these agents in CRPC.

THE PROBLEM

Our patient is a 58-year-old man who was initially diagnosed in October 2001 with adenocarcinoma of the prostate, Gleason score $4 + 4 = 8$, after receiving bilateral prostate biospies during workup of an abnormal digital rectal examination. Six months later, he began treatment with brachy-

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therapy followed by external-beam radiation therapy and goserelin administered every 3 months. He tolerated this treatment well and prostate-specific antigen (PSA) levels were undetectable. His surveillance was uneventful until January 2007, almost 5 years after initiation of treatment, when his PSA level rose to 2.1 ng/mL, which was associated with a testosterone level of 36 ng/dL. A repeat biopsy of the prostate confirmed residual adenocarcinoma. Cryotherapy was attempted. Subsequently, he was treated by his urologist with multiple hormonal therapies, including anti-androgens, ketoconazole, and prednisone. Eight months later, the PSA continued to rise to 4.5 ng/mL. Within 3 months, the PSA was 10.9 ng/mL, signifying a marked increase in the PSA velocity. Bicalutamide was added to his regimen of ketoconazole, prednisone, and goserelin, and he was then referred to our office for further management.

His past medical and surgical history was significant for diabetes mellitus, hypertension, rotator cuff injury, and two rotator cuff surgeries. He was a nonsmoker, did not drink alcohol or use recreational drugs, and had no occupational exposures to harsh chemicals or radiation. Regarding his family history, both his brother and his father died of head and neck carcinoma. His mother died of lung carcinoma. All three were heavy smokers. On review of systems, he described occasional right hip pain, but denied back pain or other symptoms suggestive of metastatic disease to the bones. He also reported mild fatigue, urinary frequency, and nocturia. He denied any incontinence, decrease in appetite, or weight loss.

Physical examination revealed an obese male (326 lb), in no acute distress and with normal vital signs. Musculoskeletal examination did not reveal any bony or muscular tenderness to palpation. Neurologic examination was also normal without any evidence of peripheral neuropathy or decreased sensation. The remainder of the examination was unremarkable.

Imaging studies obtained prior to the visit included a bone scan, which revealed minimal osseous metastatic disease. A magnetic resonance image (MRI) of the pelvis revealed a solitary 2.4-cm soft tissue mass extending to the base of his bladder, consistent with recurrent prostate adenocarcinoma.

Given his initial high risk Gleason score, the rapid PSA velocity, and lack of prior control with local therapies, it was decided that cytotoxic therapy was the most appropriate option to control the disease and to provide a survival advantage. Subsequently, he was treated with a bisphosphonate and docetaxel at standard dosing of 75 mg/m^2. Prior to starting taxotere, his PSA had had peaked to 16.8 ng/mL. The first cycle was poorly tolerated, and subsequently a schedule of 30 mg/m^2 weekly for 5 of 6 weeks was started, in addition to prednisone and leuprolide. He then tolerated the therapy well and had a dramatic improvement in his PSA, which fell to 3.8 in 4 months. He experienced mild grade I neuropathy of his toes, bilaterally, but had no other major symptoms. He completed 30 weeks (10 cycles) of docetaxel in November 2008 but continued to receive maintanence therapy with leuprolide every 3 months. On successive office visits in late 2010, his PSA again began to rise. Since January 2011, his PSA was checked monthly and the levels increased steadily from 4 ng/mL to 10.4ng/mL in only 3 months. He remains asymptomatic without obvious evidence of progression of metastatic disease.

We pose the following specific questions regarding the patient's management: (1) In retrospect, should he have been started on systemic chemotherapy in 2007, despite being asymptomatic and had minimal disease? (2) If so, should docetaxel be discontinued at 10 cycles (per TAX 327 trial) or continued, given data showing that driving PSA levels into the normal range can extend survivorship?[8] (3) At this point, should he be rechallenged with docetaxel, or considered for cabazitaxel? Abiraterone? (4) Upon restaging, what would experts recommend if minimal metastases are established? Cabazitaxel? Abiraterone? Sipuleucel-T? (5) How do we chose between abiraterone versus cabazitaxel after docetaxel failure, assuming similar efficacy, based on the lack of head-to-head comparison trials? (6) Should treatment with docetaxel continue until disease progression? If a "holiday" is given, should re-challenge be attempted now that survival data with other agents after docetaxel failure exists? Can sipuleucel-T be used after docetaxel failure? (7) Finally, in order to manage bone metastases, how long should zoledronic acid be given? How do we choose between zoledronic acid and denosumab initially, given the recent approval of the latter?

MEDICAL ONCOLOGISTS' OPINIONS

This presentation of a young man with high-risk recurrent CRPC exemplifies many of the challenges clinicians face in weighing the risks and benefits of prostate cancer treatment in the palliative setting. When the patient was referred to medical oncology, he had presumably completed a total of 3 years of neoadjuvant and adjuvant LHRH agonist therapy, which confers survival benefit in men with high-risk prostate cancer undergoing radiotherapy.[9,10] Repeat biopsy in 2007, when his PSA was first elevated, is a worthwhile practice as we always ask (and hope) that the disease is still local and curable. If workup at that time showed no evidence of systemic disease, a trial of local therapy is reasonable. Unfortunately, cryotherapy was unsuccessful in this case.

We assume that the patient received 2 or 3 years of ADT with radiation and it is interesting that his androgen level did not recover years after local treatment. Generally for a young patient, his testosterone lev-

els should recover in within 6–9 months of the last LHRH injection, but clearly there is variability. In January 2007 when his PSA was 2.1 ng/mL with testosterone of 36 ng/dL, he was technically in a stage of castration-resistant disease (testosterone <50 ng/dL). In the absence of surgical or salvage radiotherapy options, re-initiation of LHRH agonist therapy, followed by the secondary hormonal manipulations of bicalutimide, ketoconazole, and prednisone, were all reasonable. Should he have been started on systemic chemotherapy in 2007, despite being asymptomatic and had minimal disease? There is no randomized data to date to indicate that early chemotherapy will provide a clinical benefit to these patients. The ongoing phase III ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial, which randomizes men with recurrent or metastatic prostate cancer to LHRH agonist alone or LHRH agonist with six cycles of docetaxel, may provide some additional data for this question, but for now the standard remains androgen-ablation therapy. The timing of initiation of chemotherapy also still remains unclear. Typical indications for initiating chemotherapy in patients with metastatic castrate-resistant disease could be pain, constitutional symptoms, and rapidly progressive disease, particularly in visceral organs. Patients who have short responses to primary hormonal therapy or do not normalize their PSA (<4 ng/mL) may represent a poor-risk group and may need more aggressive therapy.[11,12]

The optimal number of cycles of docetaxel chemotherapy has not been well defined. Ten was the maximum allowed number of cycles in the TAX 327 study due to the control arm, which only allowed 10 cycles to minimize the cumulative risk of cardiac toxicity from mitoxantrone.[2] Nevertheless, the median number of docetaxel cycles every 3 weeks in TAX 327 was 9.5, and in the control arm of Cancer and Leukemia Group B (CALGB) 90401 was 8; however, some patients received up to 40 cycles of docetaxel therapy in this study.[13] A retrospective analysis compared outcomes of men with CRPC who received docetaxel in the TAX 327 trial and men who received docetaxel in CS-205, a randomized phase II trial where the bcl-2 inhibitor AT-101 was added to docetaxel, and allowed up to 17 cycles. There was no survival benefit if men received more than 10 cycles of docetaxel in this retrospective hypothesis-generating analysis.[14] Intermittent chemotherapy or re-challenge with docetaxel or docetaxel combination therapy has also demonstrated some efficacy but may not be used as commonly now in the cabazitaxel and abiraterone era.[15,16] With the current available active second-line agents, vigilance of cumulative treatment toxicities versus their benefit needs to be taken into consideration.

It also should be noted that the statistically significant survival benefit of first-line docetaxel over mitoxantrone has only been demonstrated in the every-3-week dosing schedule.[2] In addition, patients treated weekly experienced similar toxicity to the every-3-week dosing schedule and no survival benefit. Men who are intolerant to the every-3-week schedule at full dose may benefit from dose reduction or growth factor support. It is curious that this young man initially exhibited poor tolerance to an agent commonly given to the elderly, calling in to question the impact his obesity may have had on dose calculation and thus toxicity.[17,18]

Since there is an established survival benefit for the use of abiraterone and cabazitaxel in the docetaxel failure population, the use of either of these agents is warranted, although there is no head-to-head comparison between the two. Further studies are needed to guide us as to which patients may benefit more from abiraterone or cabazitaxel in this setting.[5–7] Prior exposure to anti-androgens, medical comorbidities, prior and ongoing toxicities of treatment (most importantly marrow reserve and peripheral neuropathy), and performance status must guide this decision. In early studies of abiraterone, men previously treated with ketoconazole had an inferior clinical response over those who were ketoconazole-naïve, and in phase III studies previous ketoconazole-treated men were excluded.[19] Since it is not clear what degree of survival benefit men previously exposed to ketoconazole would be expected to have, in these men we would favor the initial use of cabazitaxel over abiraterone. Abiraterone may have a more beneficial effect in patients with poor performance status or no previous exposure to ketoconazole and in patients with continued detection of androgens. Cabazitaxel may be more favorable in patients with high disease burden but low PSA, visceral metastatic disease, low testosterone, age <65 years, reasonable bone marrow function, and performance status <2. Dose reduction and or use of granulocyte growth factor support should be considered in all patients, especially in elderly patients and those with poor marrow reserve.

In this asymptomatic patient with minimal bone metastasis and no visceral disease, sipuleucel-T is another treatment option with overall survival benefit.[1,20] The sipuleucel-T immunotherapy for CRPC trial excluded patients who had undergone chemotherapy within the previous 3 months or systemic glucocorticoids within 28 days of enrollment; thus, at this point, this patient has had an appropriate washout.[20] In this study, 15.5% patients previously received docetaxel and were included in the overall survival analysis. What impact long-term chemotherapy and corticosteroid use may have on the yield of activated antigen-presenting cells and subsequent immune competence have not been thoroughly explored, and thus the role of immunotherapy in patients

previously treated with docetaxel remains unclear. Patients in both the sipuleucel-T and control arms experienced the same rate of disease progression and time to next treatment. While we are still defining the optimal patient population, patients who are asymptomatic or minimally symptomatic are excellent candidates for this therapy. Additional studies are underway to further evaluate the impact of chemotherapy and radiotherapy on sipuleucel-T.

Another uncertainty for supportive care in men with bony metastatic CRPC is the choice between bisphosphates and the newly approved RANKL antibody denosumab. In a phase III study of men with metastatic CRPC, denosumab every 4 weeks demonstrated a significant improvement in mean time to skeletal related events over zolendronic acid on the same schedule.[21] The rates of osteonecrosis of the jaw in the two groups were similar, but patients on the denosumab arm had a significantly higher risk of hypocalcemia. Previous studies with the same treatment arms in other solid tumors demonstrated a lower risk of renal events in the denosumab arm, especially for those with creatinine clearance <60 mL/min.[22,23] Use of densoumab in men with CRPC and bone disease is warranted; however, whether this actually makes a difference in overall survival still is not known. Due to the ease of administration and favorable toxicity profile, many are switching over to denosumab to maintain bone health. If the bone disease is minimal, less frequent dosing may be sufficient, but the optimal timing and duration of these agents have yet to be defined.

With the availability of multiple active treatment options, predictive biomarkers are needed to guide individualized therapy. Molecular regulation of androgen synthesis and the mechanisms of castration resistance, docetaxel-resistance, and potential immune system alteration after prednisone and taxane chemotherapy are areas of active research. In the ever-evolving landscape of treatment for advanced CRPC, more options are better, yet we must learn how to best use and sequence these agents for the optimal care of our patients.

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MEDICAL ONCOLOGISTS' OPINIONS

In answer to the question as to whether the patient should have been started on systemic chemotherapy in 2007 for asymptomatic and minimal extent of disease, we respond "no". Progression of disease in 2007 was determined by rising PSA alone. Presuming distant metastases were ruled out with imaging, his only evidence of disease at that time was local involvement of the prostate noted on biopsy. While it is understandable to want to address local disease with local intervention, in this case, cryotherapy, it is important to carefully select patients for this procedure.[24] With a rising PSA after cryotherapy, this patient may have had micrometastatic disease in 2007. There are no data to support the use of cytotoxic therapy in patients without radiographic evidence of metastasis; therefore, it is not recommended in this setting.[25] Given the patient's lack of both symptoms and measurable metastatic disease, we would favor secondary hormone therapy in this setting, which this patient ultimately went on to receive.

For patients with radiographic evidence of metastasis, the TAX 327 trial showed that both patients with and without pain demonstrated a survival benefit to treatment. Although there was a difference in overall survival between the groups, the magnitude of this difference is expected, given that patients with symptoms are further along in the course of their disease.[26] Based on these data, we typically reserve cytotoxic chemotherapy for patients with symptoms, visceral involvement, or evidence of rapid radiographic progression of disease.[2] Published opinion supports this practice.[27,28]

The decision to initiate or change therapy, however, should be driven by whether a patient has evidence of progressive disease. Nevertheless, defining progression in prostate cancer can be challenging. In 2008, the Prostate Cancer Clinical Trial Working Group (PCWG2) developed guidelines for the design and endpoints in clinical trials. It recommended continuing treatment for at least 12 weeks to allow for adequate drug exposure. In addition, it also recommended not modifying treatment based solely on early changes in PSA or pain without other evidence of disease progression. If bone is the only site of disease, the PCWG recommended that progression should require at least two new lesions compared to the baseline study, and confirmation of this change in a second bone scan.[29]

We can apply some of the PCWG2 guidelines in this case. If increasing PSA is the only evidence of progression, the patient could be continued on ADT alone or in combination with single-agent prednisone. This would spare him the toxicity of chemotherapy. However, he should be carefully followed with periodic clinical examinations and radiographic studies. He could be re-treated with docetaxel if he develops evidence of progressive disease.

The optimal duration of treatment with docetaxel is unclear; the benefit of treatment beyond 10 cycles has not been established in prospective clinical trials. The benefits of continued treatment (potential for longer disease control) should outweigh the risks (short- and long-term toxicity). In TAX 327, patients could receive up to 30 weeks of treatment (ten 3-week cycles). The median number of 3-week cycles given was 9.5 (28.5 weeks), suggest-

ing that the treatment was well tolerated. However, 11% of patients in the every-3-week group discontinued treatment due to adverse events, which included fatigue, musculoskeletal or nail changes, sensory neuropathy, and infection.[2] Therefore, while some patients with responding disease may derive benefit from additional cycles (pain control, control of visceral disease), patients who are developing treatment related toxicity may benefit from a treatment "holiday."

The Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT) trial of weekly docetaxel given 3 of every 4 weeks with or without high-dose calcitriol allowed patients who reached a PSA ≤4 ng/mL to go on a chemotherapy holiday. Treatment was resumed if the PSA rose by ≥50% and was ≥2 ng/ml or there was other evidence of disease progression. Eighteen percent started on a chemotherapy holiday; the median duration was 18 weeks. A total of 45.5% of patients demonstrated PSA declines after resuming treatment. Another 45.5% demonstrated PSA stability. These findings suggest that chemotherapy holidays are appropriate and necessary for a significant number of patients and avoid the toxicity of continuous treatment. However, as the authors note, the optimal appropriate PSA value at which to initiate a chemotherapy holiday has not been established[30] and requires clinical judgement. We recommend the use of patient performance status, toxicity assessment, and results of imaging to guide the decision-making regarding the resumption of docetaxel.

If the current patient progresses following treatment with docetaxel, he may be a candidate for two new treatments: abiraterone and cabizataxel.How do we chose between them? There are currently no data on the optimal sequencing of abiraterone versus cabazitaxel after docetaxel failure; this decision should be based on the toxicity profile and patient preference. For many patients, abiraterone may be associated with a lower risk of toxicity. Abiraterone is an oral agent given in combination with prednisone that blocks cytochrome P450 (CYP 17), a critical enzyme in testosterone synthesis. As previously stated, patients with docetaxel-refractory disease who received abiraterone and prednisone had a 3.9-month longer median survival compared to those who received the placebo and prednisone (14.8 *v* 10.9 months; hazard ratio, 0.65; 95% confidence interval [CI], 0.54–0.77; $P < .001$). Fatigue was the most common side effect, which occurred in equal numbers in both arms. Patients who received abiraterone were more likely to experience adverse events related to elevated mineralocorticoid levels due to CYP 17 blockade. These included fluid retention, hypokalemia, and hypertension. Most of these events were grade 1 and 2.[7]

Table 1. Examples of Drugs To Be Used Cautiously With Abiraterone

CYP2D6 Substrates	CYP3A4 Inhibitors	CYP3A4 Inducers
Carvedilol	Amiodarone	Nafcillin
Metoprolol	Clarithromycin	Phenobarbital
Propanolol	Fluconazole	Phenytoin
Codeine	Verapamil	Pioglitazone
Tramadol	Erythromycin	
Hydrocodone		

Note. This list is does not include all potential interactions; physicians should review a patient's medication list and discuss with potential drug interactions with his pharmacist and other physicians.

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6 and a substrate of CYP3A4. Therefore, substrates of CYP2D6 and strong inhibitors and inducers of CYP3A4 should be avoided or used with caution. This includes broad classes of medications that are frequently prescribed in elderly patients, such as tricyclic anti-depressants, beta blockers, anti-arrhythmics, and macrolide antibiotics. Medical oncologists must take a detailed medication history; patients will receive their abiraterone from a specialty pharmacy that may be unfamiliar with their other prescription medications. Examples of substrates of CYP2D6 and inhibitors and inducers of CYP3A4 are shown in Table 1.[31,32]

Cabazitaxel is a novel tubulin-binding taxane that is given intravenously. The TROPIC study randomized men whose disease progressed during or after docetaxel to receive either cabazitaxel or mitoxantrone. All subjects received prednisone. There was a 2.4-month improvement in median overall survival in the group that received cabazitaxel (15.1 *v* 12.7 months; hazard ratio, 0.70; 95% CI, 0.59–0.83; $P < .0001$).[5] The objective response rate (Response Evaluation Criteria in Solid Tumors [RECIST]) was higher in the group that received cabazitaxel (14.4% *v* 4.4%), but there was no difference in the pain response rate (9.2% *v* 7.7%). Grade 3 and higher neutropenia (82% *v* 58%), diarrhea (6% *v* <1%) and febrile neutropenia (8% *v* 1%) were higher in the cabazitaxel group and required dose reduction In addition to these adverse events, 4.8% of patients treated with cabazitaxel had a treatment-related death, of which nearly half were attributed to neutropenia complications. Consequently, oncologists should consider dose modification and the use of prophylactic granulocyte colony-stimulating factor (G-CSF)

to mitigate severe neutropenia and the risk of infection.[33]

How do we choose between bisphosphonates in managing bone metastases? Denosumab is a RANK ligand inhibitor that was recently approved for men with metastatic CRPC to bone. When compared to zolendronic acid, denosumab was shown to delay the onset of skeletal-related events (median, 17.1 *v* 20.7 months; hazards ratio, 0.70; 95% CI, 0.59–0.83; $P < .0001$). However, there was no difference in overall survival or time to disease progression. Unlike zolendronic acid, denosumab does not need to be adjusted for changes in creatinine. Rates of osteonecrosis of the jaw were similar in both arms. However, hypocalcemia was seen more frequently in patients receiving denosumab, so electrolyte monitoring (calcium and phosphorus) is still necessary.[21]

Whether the modest benefit of delaying SRE *without* a corresponding benefit in survival justifies the significantly higher cost of denosumab is the subject of significant debate.[34] While a discussion of the "value" of these treatments is beyond the scope of this column, oncologists may need to take cost into account, particularly in patients who face high copayments for medications.

There are no prospective data regarding the optimal duration of treatment with either agent. The current practice is to treat the patient indefinitely provided he is tolerating therapy.

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MEDICAL ONCOLOGIST'S OPINION

The case presented by Drs Beach and Somer highlights the remarkable recent progress that has been made in the treatment of patients with metastatic CRPC. If I had evaluated this patient in 2007 when he presented with metastatic high-grade CRPC and a rapidly rising serum PSA, I also would have initiated cytotoxic chemotherapy with docetaxel plus prednisone. I would have stopped after 10 cycles, giving the patient a "chemotherapy holiday" to recover from any cumulative effects of treatment. Remarkably, this patient experienced freedom from disease progression for almost 2 years. I would like to be bold here and state that this is about "as good as it gets" with chemotherapy for metastatic CRPC: an excellent response to chemotherapy, minimal toxicity, and a relatively long time to disease progression. Given these facts, my inclination would be to retreat the patient with docetaxel plus prednisone. Recently, investigators from France[35] and Italy[36] reported promising retrospective studies of docetaxel re-treatment in patients who previously responded to this agent. Alternatively, initiation of either cabazitaxel or abiraterone would be reasonable. In the patient who demonstrated previously docetaxel-sensitive disease, there are no randomized data comparing re-treatment with docetaxel versus treatment with one of the newer agents. Likewise, there is no randomized study comparing cabazitaxel and abiraterone in the docetaxel-pretreated patient. Therefore the choice needs to be based on a thorough discussion with the patient of the treatments, their associated toxicities, and their costs. In my opinion, the benefit of sipuleucel-T in this setting is less clear. Recall that a minority of patients in the definitive randomized trial had received prior chemotherapy and, in these patients, the impact of sipuleucel-T on survival was not statistically significant.[20] Finally, my preference would be to initiate denosumab given the recent study demonstrating improved time to first skeletal-related event in patients with metastatic CRPC compared to zolendronic acid.[7] In sum, patients with metastatic CRPC and the oncologists who care for them have an exciting armamentarium of new treatment options that positively impact both survival and quality-of-life.

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UROLOGIC ONCOLOGIST'S OPINION

This 58-year-old male with initially T2 Gleason score 4 + 4 = 8 adenocarcinoma of the prostate received brachytherapy followed by external-beam radiation therapy and adjuvant hormone therapy in 2001. In January 2007, he was noted to have biochemical failure with a rising PSA. Despite the addition of combined androgen blockade, he progressed with further elevation of his PSA. Imaging studies included a bone scan, which revealed minimal osseous metastatic disease, and a MRI of the pelvis, which revealed a 2.4-cm soft tissue mass extending to the base of his bladder, consistent with recurrent prostate adenocarcinoma. He was then started on cytotoxic therapy with bisphosphonate and docetaxel. His PSA declined from a peak of 16.8 ng/mL to 3.8 ng/ml in 4 months. He completed 10 cycles of docetaxel by November 2008, and then was maintained on hormone therapy with a LHRH agonist.

Beginning in late 2010, his PSA began to rise and by the spring of 2011 was elevated to 10.4 ng/mL. Fortunately, he remained asymptomatic without obvious evidence of disease progression. The question at this time is what therapy should be offered to this individual.

I would submit that this gentleman would be an excellent candidate for sipuleucel-T infusions. Sipuleucel-T is an autologous cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T is infused at approximately 2-week intervals, for a total of three doses.[37] It received US Food and Drug Ad-

ministration approval in April 2010 for the treatment of metastatic CRPC in asymptomatic or minimally symptomatic men.

In the pivotal phase IIIIMPACT trial (D9902B), 512 subjects were randomized 2:1 to receive sipuleucel-T (n = 341) versus control (n = 171). The primary endpoint of overall survival was analyzed by means of a stratified Cox regression model adjusted for baseline levels of serum PSA and lactate dehydrogenase. Subjects randomized to sipuleucel-T on the IMPACT trial had a 22% reduction in the risk of death compared to control (hazards ratio, 0.78 [95% CI, 0.61–0.98]; $P = .03$). This treatment effect was also demonstrated with an unadjusted Cox model and log-rank test analysis (hazards ratio, 0.77 [95% CI, 0.61–0.97]; $P = .02$). The median survival advantage was 4.1 months (25.8 months for sipuleucel-T subjects *v* 21.7 months for control subjects). Survival probability at 36 months was 31.7% in the sipuleucel-T arm versus 23.0% in controls.[20]

Sipuleucel-T is well tolerated by patients. In the IMPACT trial, adverse events reported at least twice as frequently in the sipuleucel-T group included chills, pyrexia, headache, myalgia, influenza-like symptoms, and hyperhidrosis.[38] These events generally occurred within 1 day of infusion, were generally of grade 1 or grade 2 severity, and usually resolved within 1 to 2 days, with the exception of myalgia and influenza-like illness, which generally resolved within 14 days of infusion.

Approximately 19.6% of patients in the treatment arm of the IMPACT trial had received chemotherapy prior to their enrollment versus 15.2% in the control arm. Since beginning clinical infusions in my practice in June 2010, approximately 50% of the patients had already received docetaxel. PSA cannot be used as a marker for disease control with sipuleucel-T. Rather, the clinical course needs to be assessed with follow-up imaging studies including bone scan and MRI.

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DISCUSSION

After thorough discussion with our patient regarding the risks and benefits of the various treatments, we decided to treat him with abiraterone. Prior to initiation of the drug, his PSA had climbed to 23 ng/dL. He is currently tolerating the treatment well with only minimal side effects of hot flashes and sweats. After approximately 4 months, he has had an excellent PSA response; the current level is 11 ng/dL.

From expert opinion, it is clear that while there is some consensus about the efficacy of the treatment options, there remains discordance as to the next best step in management. Indeed, there is no right or wrong answer at this time. Therapeutic algorithms will likely change as newer agents become available in our armamentarium, and may be used earlier in the course of disease so as to change our treatment paradigm. However, the one certainty that we all can agree upon is that both clinicians and their patients are now enjoying many new treatment options for this disease.

We thank our contributors for their excellent discussions, and encourage our readers to submit their further opinion in this venue.

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