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Metastatic Prostate Cancer: A Case Study

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STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

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Metastatic Prostate Cancer: A Case Study

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INTRODUCTION

Prostate cancer remains the second leading cause of death in men in the United States as of 2012. It is estimated that prostate cancer affected more than 241,000 new men in 2012, with 15% of these patients presenting with advanced disease.[1] As one would expect, compared to localized prostate cancer, metastatic disease remains the more challenging type to treat. In 1941 Huggins and Hodges demonstrated the dependence of prostatic tissues on androgens and from this work hormonal therapy was developed as the primary treatment for metastatic prostate cancer.[2] Since then, significant progress has been made in the treatment of metastatic prostate cancer, including advances in androgen deprivation therapy and in the treatment of castration-resistant prostate cancer (CRPC), with many advances yet to come. CPRC has been an exciting topic for recent research and advancement, as our understanding of how prostate cancer utilizes very low levels of androgen has evolved considerably.

CASE PRESENTATION

A 69-year-old man is referred to a urologist by his primary care physician after recent testing reveals a prostate-specific antigen (PSA) level of 4.3 ng/mL. The urologist performs a biopsy and the pathology shows Gleason 3+3 prostate cancer in 3/12 cores. After considering his options, the patient elects to undergo active surveillance. The following year, the patient undergoes a repeat biopsy, which again shows Gleason 3+3 in 3/12 cores, and his PSA remains stable. Two years after the original diagnosis, his PSA is found to be 11 ng/mL. He denies any new symptoms of bone pain or weight loss at that time. Due to the rapid PSA doubling time, a repeat prostate biopsy is again performed, which now shows Gleason 4+5 disease.

- **What factors predict progression?**
- **How should this patient be restaged?**

Initial evaluation after diagnosis of prostate cancer should include pretreatment parameters and possible imaging depending on disease classification. These pretreatment parameters include PSA, Gleason grading, and digital rectal exam findings. D'Amico and colleagues used these 3 parameters to separate patients into low-risk, intermediate-risk, and high-risk classifications, which were shown to predict clinical outcomes.[3,4] Patients with low-risk (clinical stage T1 to 2a, PSA $\leq$10 ng/mL, and Gleason score $\leq$6), intermediate-risk (stage T2b, PSA >10 but <20 ng/mL, or Gleason score 7), and high-risk disease (stage T2c, PSA >20 ng/mL, or Gleason score 8 to 10) were found to have a disease-free survival of 83%, 46%, and 29%, respectively, at 10 years.[3,4] Most primary treatments are now guided by this classification system.

During surveillance after initial treatment, it is important to screen for progression/recurrence. Several factors predicting progression have been identified. In 1999, Pound et al followed 1997 men who underwent surgical resection of their primary tumor of clinically localized prostate cancer for a median duration of approximately 5 years (0.5–15 years).[5] All patients who received adjuvant hormonal therapy were excluded from the study (11/1997). The patients were followed until they were found to have biochemical recurrence (15%), defined as PSA greater than 0.2 ng/mL, metastasis (34% of those with recurrence), or death (14.5% of those with recurrence). The time to each of these outcomes was 3.3 years from the time of surgery and 8 years and 11 years from time of PSA elevation, respectively. Pound and colleagues found that predictors of progression to metastases are PSA doubling time (<10 months), Gleason score (8–10), and time to biochemical recurrence (<2 years).

Common sites of metastatic disease include the pelvic lymph nodes and bone (vertebrae, proximal ends of long bones, pelvis, and skull), but other organs can be involved, such as the lung, bladder, rectum, liver, and adrenal gland.[6] The primary areas of metastases therefore dictate the staging work-up for high-risk prostate cancer or for patients with concern for metastatic disease. The mainstays of the metastatic work-up include a radionuclide bone scan and a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis, with or without a chest radiograph. Patients recommended for further imaging include those with a PSA greater than 20 ng/mL, a Gleason score of 8 to 10, clinical stage T3 or T4, clinical stage T1 or T2 with a nomogram probability of lymph node metastases greater than 20%, or presence of clinical symptoms concerning for metastatic disease.[7,8] Plain films have a lower sensitivity and are usually only used to confirm a positive bone scan if a patient is at low risk for bone metastasis. There are currently no recommendations on the use of MRI spectroscopy or combined MRI as these techniques are still under clinical evaluation. Finally, if a patient still has intact prostatic tissue, a biopsy may be indicated to assess for local advancement.

CASE PRESENTATION CONTINUED

A CT scan of the abdomen and pelvis and a bone scan are performed, which reveal diffuse pelvic and retroperitoneal lymphadenopathy with resultant bilateral hydronephrosis. This is accompanied by an increase in his baseline serum creatinine from 0.8 to 2.0 mg/dL. No bone metastases are seen on the bone scan. Bilateral ureteral stents are placed and he is initiated on bicalutamide and leuprolide, as well as calcium and vitamin D supplementation. He continues to receive leuprolide every 3 months, and bicalutamide is discontinued after 2 weeks. His PSA is checked routinely every 3 months and his stents are exchanged every 6 months.

ANDROGEN DEPRIVATION THERAPY

Endogenous gonadotropin-releasing hormone (GnRH) is released in a pulsatile manner from the hypothalamus, which in turn stimulates the anterior pituitary to release luteinizing hormone (LH). LH targets the testes to release testosterone, which stimulates growth of prostatic epithelium.[2] Most of the therapies for metastatic prostate cancer have taken advantage of the androgen axis by decreasing testosterone to castrate levels, as pioneered by Huggins and Hodges.

Androgen deprivation therapy (ADT) has evolved over many years. Previously, bilateral orchiectomy was the primary modality for castration and therefore treatment of metastatic prostate cancer. Although this is still a primary treatment of metastatic prostate cancer, other opportunities were pursued using the hypothalamic-pituitary-gonadal axis to refine therapy. Diethylstilbestrol was the first agent to be used as medical hormonal therapy.[9] Diethylstilbestrol, with its estrogen component, was found to have a very potent negative feedback mechanism on LH secretion. Unfortunately, this drug was also found to have significant cardiac side effects, limiting its routine use and prompting further refinements in ADT. In 1971 Schally and colleagues isolated the luteinizing hormone-releasing hormone (LH-RH), which then gave way to the production of synthetic LH-RH agonists and later antagonists.[10] The LH-RH agonist triggers an initial surge of LH and testosterone, followed shortly afterwards by a loss of pituitary phasic stimulation due to negative feedback mechanisms. The LH and subsequently testosterone levels then drop dramatically to castrate levels (testosterone <50 ng/dL). The initial surge, or "flare," can cause significant secondary symptoms in patients with advanced local or metastatic disease, including bladder outlet obstruction, hot flashes, or, in patients with bone metastases, significant bone pain and spinal cord compression. The co-administration of antiandrogens for the first 2 weeks negates this effect, and so anti-androgens are often added as a prophylactic measure.

Advances also have been made to produce synthetic LH-RH agonists in long-acting depot forms that last several months rather than only days, as was the case with their original preparation. Forms of LHRH agonists used today are leuprolide, goserelin, triptorelin, and histrelin.

LH-RH antagonists were developed later and are still under evaluation. Degarelix, a LH-RH antagonist, was recently studied in a phase III trial versus leuprolide to provide data on efficacy and safety. Klotz and colleagues randomly assigned 610 patients with hormone-sensitive prostate cancer to receive either degarelix or leuprolide once per month for 1 year.[11] This study showed that degarelix reduced testosterone and PSA levels more rapidly than leuprolide and kept these values suppressed for the entire study period. Side effects were minimal, including arthralgias, chills, and urinary tract infections. The study authors concluded that degarelix was not inferior to leuprolide and could be used safely for ADT without the concern of a flare.[11] An extension of this study showed that degarelix improved PSA progression-free survival as compared to leuprolide and suggested that degarelix delayed progression to castrate-resistant disease.[12] Not only was time to PSA failure or death significantly longer in 25% of patients that received degarelix as compared to leuprolide (514 vs 303 days; $P = 0.01$), but PSA failure rates were also lower in those who received degarelix versus leuprolide ($P = 0.04$).[13,14] Degarelix has also been suggested to help in controlling skeletal metastases due to its prolonged suppressive effect on serum alkaline phosphatase (S-ALP).[15] S-ALP is used as a serum marker for bone turnover and for progression of skeletal metastases. In a subanalysis, Schröder et al found that degarelix suppressed S-ALP below baseline levels, and maintained this suppression throughout the year-long study, unlike leuprolide.[15] The authors postulated that this may prove beneficial in those patients with impending cord compression due to extension of skeletal metastases.

In regards to symptom control, degarelix has been shown in the animal model, at noncastrate levels, to shrink benign prostatic tissue.[16] This led to a randomized, parallel-arm, active-controlled, open-label, multicenter trial by Axcrona and colleagues comparing degarelix (240/80 mg) monthly injections with monthly goserelin (3.6 mg) for the improvement of lower urinary tract symptoms (LUTS), reduction of total prostate volume, and improvement in quality of life.[17,18] Bicalutamide was added to the goserelin regimen for the initial 28 days. Treatments were given for a total of 12 weeks and resulted in a greater decrease in the International Prostate Symptom Score (IPSS) for the degarelix-treated patients as compared to the goserelin-treated patients, and this decrease was statistically significant in those patients with a baseline IPSS greater than 13 (-6.7 ± 1.8 versus -4.0 ± 1.0). The reduction in total prostate volume was equal between both arms.

Other antagonists that have been produced include abarelix and cetrorelix. While few studies have evaluated the comparative effectiveness of various ADT modalities, they are commonly believed to be equivalent with regard to effectiveness.

Other strategies used for ADT include inhibition of the androgen ligand-receptor interaction. Antiandrogens are separated into steroidal and nonsteroidal types. Cyproterone acetate is the only steroidal antiandrogen.[19] It not only inhibits peripherally at the receptor level, but also centrally due to its steroidal effect. Side effects, however, limit its use, including gynecomastia, fulminant hepatotoxicity, and severe cardiovascular complications in up to 10% of patients.[20,21] The nonsteroidal agents (flutamide, bicalutamide, nilutamide) do not have a central inhibitory effect and therefore allow LH and testosterone levels to increase slightly, which some speculate may help ameliorate erectile dysfunction and other side-effects associated with its steroidal counterpart.[22] Erectile function may not be preserved as much as is commonly believed, however, with only 20% of patients found to have function while on flutamide.[23] Side effects from nonsteroidal antiandrogens include gynecomastia, erectile dysfunction, gastrointestinal toxicity, diarrhea (flutamide), and liver toxicity (ranging from reversible hepatitis to fulminant hepatic failure). Because of the risk of hepatic failure, routine liver function testing is recommended with the use of these agents.[24–26]

Antiandrogens, as previously discussed, can be used in conjunction with LH-RH agonists in combined androgen blockade. A meta-analysis performed by Samson and colleagues that analyzed 21 trials showed combined androgen blockade does not improve survival at 2 years, but it may increase 5-year median overall survival by a modest amount.[27] Some urologists believe that combined blockade can be detrimental to the disease process. This phenomenon was first described in 1993 by Kelly and Scher, who found that when using combined therapy, it is possible for the antiandrogen to act as an agonist to the androgen receptor and therefore cause tumor cell proliferation.[28] It is postulated that this occurs due to mutations in the androgen receptor. When the antiandrogen is removed, the PSA decreases and at times there is objective tumor response

Table 1. Available Hormone Therapies

Type	Therapy	Dose	Advantages	Adverse Effects
Surgery	Bilateral orchiectomy	NA	Cost	Surgical procedure, loss of testicles
Estrogen	Diethylstilbestrol	Oral	Cost	Increase clot formation, CV side effects
Antiandrogens	Bicalutamide	50 mg orally daily	Easily taken as pill	Hepatotoxicity, gynecomastia, CV complications
	Flutamide	250 mg orally 3 times daily	Cost	
	Nilutamide	300 mg orally daily x 1 month then 150 mg orally daily		
	Cyproterone acetate (steroidal)	100 mg orally 3 times daily		
LH-RH agonist	Leuprolide	7.5 mg IM monthly; every 3-, 4- , and 6-month depot formulations available	Comes in depot forms	LH surge, must add anti-androgen
			Most widely studied	Not for those with impending spinal compression, worsening LUTS
	Goserelin	3.6 mg SC implant monthly		
	Triptorelin	3.75 mg IM monthly; every 3- and 6-month depot formulations available		
	Histrelin	50 mg subcutaneous implant yearly		
LH-RH antagonist	Degarelix	240 mg subcutaneous induction then 80 mg SC monthly	No LH surge	Allergic reaction (abarelix)
			Decrease LUTS	Pain at injection site
	Abarelix (taken off market)		Improve PSA progression free survival	Urinary tract infections
				Arthralgias, chills

CV = cardiovascular; IM = intramuscularly; LH = luteinizing hormone; LH-RH = luteinizing hormone-releasing hormone; LUTS = lower urinary tract symptoms; PSA = prostate-specific antigen; SC = subcutaneous.

as well.[29–31] This phenomenon is known as the "antiandrogen withdrawal phenomenon"; unfortunately, there is no evidence that it has a survival benefit. **Table 1** provides a summary of available hormone therapies.

Timing of ADT

There are uncertainties regarding duration and timing of ADT, either alone or when combined with radiotherapy. In locally advanced prostate cancer or cancer at high risk of distant metastasis, several studies have shown a benefit to long-term treatment when combined with radiotherapy.[32,33] In a study by Bolla and colleagues, survival outcome was measured for patients with locally advanced prostate cancer who received 6 months versus 3 years of ADT combined with radiation therapy.[34] The study showed the superiority of long-term hormonal therapy in overall survival. The question of when to start ADT in the setting of biochemical PSA recurrence remains. If a patient presents with metastatic cancer, immediate androgen suppression is indicated, but what if the patient has already undergone primary treatment? Messing et al found that starting ADT early versus late for patients with lymph node–positive disease at the time of prostatectomy significantly improved survival outcome (13.9 months versus 11.3 months).[35,36] But for locally advanced prostate cancer (high risk for recurrence), does one start ADT when biochemical failure is first suspected (early), or when objective signs of metastatic disease become apparent (late)? Studies support the use of early hormonal therapy to delay the time to metastatic disease.[37,38] The use of immediate ADT in treatment of locally advanced prostate cancer has been shown to improve cancer-specific survival, but not overall survival.[39] Interestingly, in men deemed not suitable for local treatment, immediate ADT may improve overall survival but not prostate cancer-specific survival.[40]

Intermittent versus Continuous Hormone Therapy

The utility of intermittent hormone therapy compared to continuous therapy continues to be studied. Due to the side-effects of hormonal therapy and increased costs, many have proposed the use of intermittent hormonal therapy to maintain androgen deprivation while balancing quality of life and cost. This form of treatment allows recovery of testosterone during off-treatment periods. It has also been shown in preclinical animal models (Shionogi breast cancer tumor, LNCaP prostate cancer tumor) that exposure to intermittent androgen deprivation may delay the time to androgen-refractory cancer growth.[41,42] For these reasons, randomized trials have been underway to study the efficacy of intermittent hormonal therapy.[43,44] In the study by Mottet et al, 176 metastatic patients were randomized in a 1:1 fashion to continuous and intermittent ADT after undergoing a 6-month induction period of ADT and achieving a PSA value of less than 4 ng/mL. The intermittent cycle began when a patient's PSA rose to greater than 10 ng/mL and was stopped when PSA was less than 4 ng/mL. PSA levels were checked monthly and follow-ups were scheduled every 3 months. Median survival (52 versus 42 months) and progression-free survival (15.1 versus 20.7 months) were not statistically different between the continuous and intermittent arm. Interestingly, the symptom and functional scales also did not show a significant difference between the 2 groups.

In a randomized trial by Calais de Silva and colleagues using a cohort of 626 patients, the results also showed no difference in overall survival between the intermittent and continuous arms. However, quality of life was affected significantly more in the continuous arm due to a higher rate of side effects, including erectile dysfunction, hot flashes, headache, gynecomastia, and skin complaints. Calais de Silva used similar cut-off points to reinitiate therapy. After an induction period of ADT and a PSA level of less than 4 ng/mL or less than 80% of the initial value was reached, the patients were randomized and therapy was stopped in the intermittent arm or continued in the continuous arm. ADT was reinitiated when the PSA level rose to greater than 10 ng/dL for those that went below 4 ng/mL previously, or if the PSA rose 20% or more above the nadir value.

Recently, Crook and colleagues performed a noninferiority randomized trial that compared intermittent with continuous hormone therapy in patients with biochemical recurrence after salvage or primary radiotherapy for prostate cancer.[45] It showed intermittent therapy was noninferior to continuous therapy with respect to overall survival. A total of 1386 patients were randomly assigned to the intermittent therapy arm (690) and the continuous therapy arm (696). Median follow-up was 6.9 years, with median overall survival of 8.8 years in the intermittent-therapy group versus 9.1 years in the continuous-therapy group (hazard ratio for death, 1.02; 95% confidence interval [CI], 0.86 to 1.21). A similar intermittent treatment protocol was used in the Mottet trial.[43] Hussain and colleagues also performed a noninferiority study comparing intermittent to continuous hormone therapy.[46] The co-primary end-points were overall survival and quality of life differences at 3 months. Their study randomly assigned 1535 patients with a median follow-up period of 9.8 years. Median survival was 5.8 years in the continuous-therapy arm and 5.1 years in the intermittent-therapy arm (hazard ratio for death with intermittent therapy, 1.10; 90% CI, 0.99 to 1.23). They were unable to conclude that intermittent therapy was noninferior to continuous therapy with respect to survival and found their results to be inconclusive. However, intermittent therapy was associated with better erectile function and mental health ($P < 0.001$ and $P = 0.003$, respectively) at month 3 but not thereafter. Intermittent therapy protocols have yet to be standardized and are not considered to be standard therapy.

Side Effects

Androgen deprivation therapy has many side effects and potential risks. It has been found to decrease lean muscle mass and increase fat mass.[47] The most common side effects are hot flashes, headaches, and erectile dysfunction. Hot flashes affect 50% to 80% of patients.[48,49] Numerous compounds have been used to abate hot flashes, including megestrol acetate, estrogens, selective serotonin reuptake inhibitors (SSRIs), and gabapentin.[50–53] Although libido is severely diminished, up to 17% of men undergoing ADT may still maintain an erection adequate for intercourse.[54]

In October 2010, the FDA issued a warning to be placed on the product labeling of LH-RH agonists highlighting an “increased risk of diabetes and certain cardiovascular diseases including heart attack, sudden cardiac death and stroke” among patients taking these agents. This warning was based on several retrospective studies.[55–57] Keating et al found that the use of LH-RH agonists is associated with a 44% increased risk of diabetes, 16% increase in sudden cardiac death, and 11% increase in myocardial infarction when looking at the national SEER-Medicare database. However, in a meta-analysis that included a total of 4141 patients with nonmetastatic disease from 8 randomized trials, no significant increase in cardiovascular death was seen in those receiving long-term hormone therapy.[58] Currently, this topic remains controversial. It appears prudent to be aware of the potential risks and monitor patients at risk of or with current cardiovascular disease who will be placed on this therapy.

Other adverse effects include osteoporosis and subsequent skeletal-related events (SREs) such as bone fracture, insulin resistance and risk for diabetes, vasomotor instability, and cognitive dysfunction. ADT decreases bone mineral density (BMD), and prolonged duration of therapy increases the risk of clinical fractures.[59] Smoking cessation, weight-bearing exercise, and vitamin D and calcium supplementation can help improve BMD. Daily supplementation of calcium (1200 to 1500 mg/day) and vitamin D (400 IU/day) is recommended by the National Institutes of Health.[60] Algorithms can also be used to predict the chance of fracture, such as the FRAX algorithm from the World Health Organization.[61]

Several medical therapies have been developed to prevent loss of BMD and to prevent SREs associated with the use of ADT. Bisphosphonates such as zoledronic acid were the first intervention to be used for this purpose. These medications induce apoptosis of osteoclasts and inhibit certain osteoclast cellular pathways. In turn, they stop bone resorption and can increase BMD. The FDA approved the use of zoledronic acid in 2002 for the prevention of SREs in patients on ADT with metastatic prostate cancer to the bones after 3 large phase III trials showed its efficacy for such patients.[62–64] Zoledronic acid is an intravenous medication that is given monthly and is shown to prevent SREs and improve bone pain in this setting. The other FDA-approved medication for the prevention of SREs in metastatic prostate cancer is denosumab. Denosumab is a RANK (receptor activator of nuclear factor kappa-B) ligand monoclonal antibody that inhibits osteoclast activity through its competitive binding of RANK ligand. It is given as a subcutaneous injection every month. Denosumab was FDA-approved in November 2010 for the prevention of SREs in patients with metastatic prostate cancer, and in September 2011 for patients with nonmetastatic/high-risk prostate cancer on ADT to increase bone mass. In a study comparing denosumab with zoledronic acid, denosumab showed superiority in delaying time to SRE (20.7 months versus 17.1 months, $P = 0.008$).[65] An important adverse effect of these medications is osteonecrosis of the jaw in patients who have chronic dental issues, seen in 1% to 2% of patients. Hypocalcemia was noted more often with denosumab, but most adverse events were minor and similar between the 2 therapies. While there remains no standard protocol, performing a baseline dual-energy X-ray absorptiometry (DEXA) scan before starting long-term ADT and then every 1 to 2 years is recommended. Use of plain film X-rays for suspected fractures and nuclear bone scans (99m-technetium bone scintigraphy) to evaluate for new bone metastases are also recommended.[66]

CASE PRESENTATION CONTINUED

One year after starting ADT, the patient starts to complain of pain in his right hip and has persistent weight loss. A repeat bone scan shows uptake in the right sacrum and iliac crest consistent with bony metastatic disease. Restaging CT scans show retroperitoneal lymphadenopathy and his PSA level continues to climb despite being on ADT. His PSA level is now 14.3 ng/mL.

- **How would this patient's disease stage be defined?**
- **What are the options for therapy now that he continues to progress? Should ADT be continued?**

CASTRATION-RESISTANT PROSTATE CANCER

This patient is now at the metastatic castration-resistant stage. CRPC, previously termed hormone-refractory or androgen-independent prostate cancer, is defined as cancer progression despite castrate levels of testosterone. It has always been clear that progression despite castration is ultimately inevitable. Previously it was thought that alternate stimulation of prostate cancer cells unrelated to the androgen axis brought about this resistance. Recent research has shown that there are multiple pathways along the androgen axis, such as increased androgen receptor activity and autocrine production of testosterone, which remain active in the presence of very low (castrate) androgen levels.[67,68] It is thus important to verify castrate levels of testosterone in men who are progressing, despite apparently adequate treatment with ADT. Due to the overactivity of the androgen receptor, ADT (LH-RH agonists, antiandrogens) is continued throughout progression to CRPC, to avoid overstimulation of the receptors. Treatment modalities for CRPC patients now include chemo-

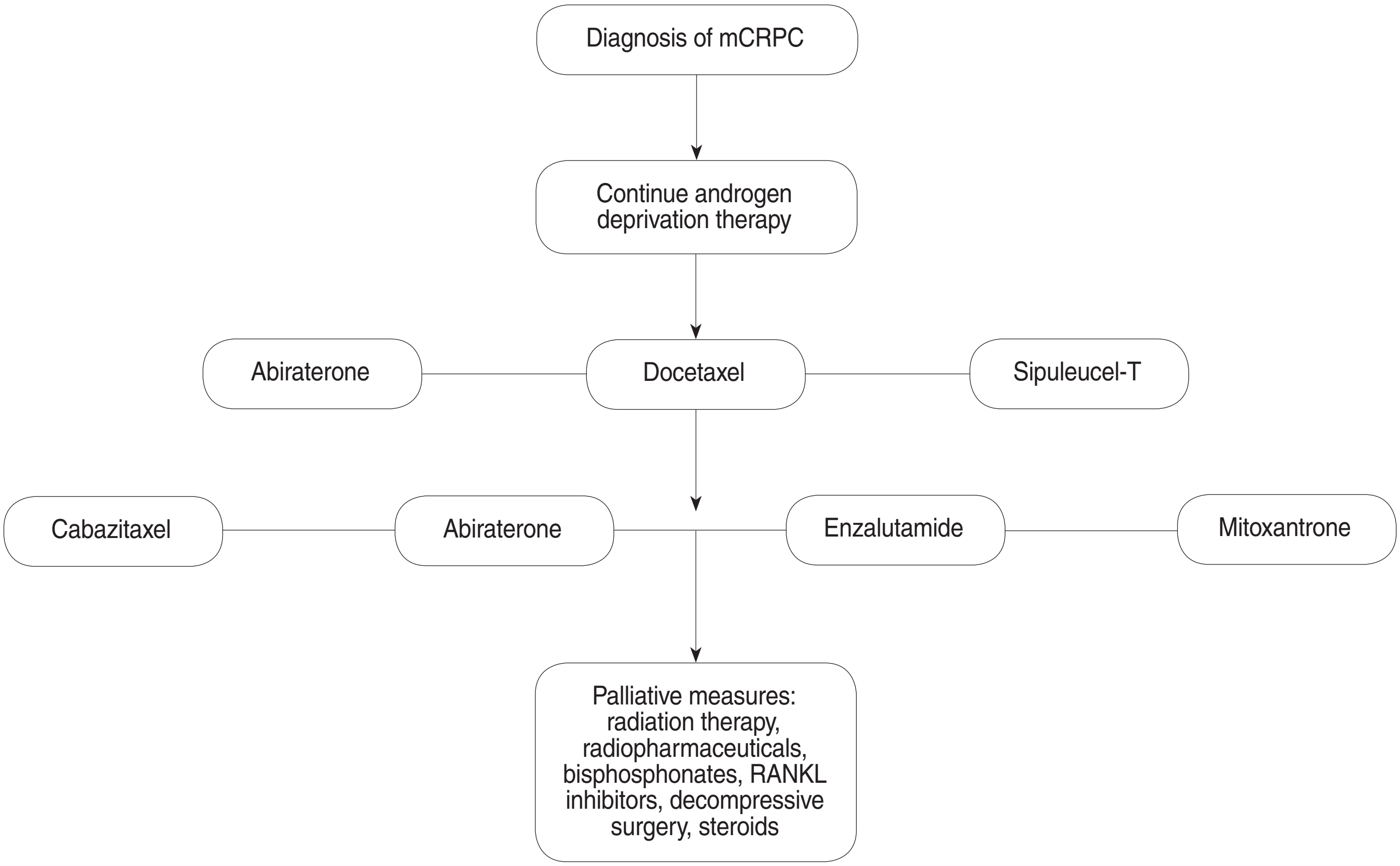

Figure. Treatment options for metastatic castration-resistant prostate cancer (mCRPC).

therapeutics, immunotherapy, alternate androgen deprivation, and bone-modulating therapies for metastatic disease (**Figure**).

Treatment Options

In 1997 the FDA approved mitoxantrone and prednisone for the treatment of symptomatic, metastatic prostate cancer. This came after a study of 161 patients by Tannock et al showed that mitoxantrone and prednisone improved quality of life and palliative measures in patients. Importantly, it did not affect overall survival.[69] In 2004 the chemotherapeutic agent docetaxel was approved for use in metastatic prostate cancer based on significant improvement in overall survival compared to mitoxantrone, as well as improvement in pain scores and quality of life. This was the first agent to show a survival benefit for CRPC. The approximate overall survival benefit was 3 months.[70–72] Although the benefit was modest, docetaxel was the first agent for CRPC patients which appeared to impact the disease course. Mitoxantrone remained a second-line treatment, especially for symptomatic patients.

Another promising approach to CRPC therapy is immunotherapy, which is currently approved as first-line therapy. Hypotheses of an immune response controlling prostate cancer cells became widespread in the late 1990s.[73] Sipuleucel-T is one of many immunotherapeutics developed against CRPC, and currently the only one with FDA approval. Dendritic cells harvested from a patient's blood via leukopheresis are used as antigen-presenting cells. These cells are loaded with a recombinant fusion protein (prostatic acid phosphatase + granulocyte-macrophage colony-stimulating factor) and then re-infused into the patient. This new cell activates T cells via class I and class II HLA molecules, which are then ready to attack the prostate cancer cells. The formation of the antigen+antigen-presenting cell is done at a central processing area, and this process is performed 3 times over 4 weeks. Two phase III trials have evaluated sipuleucel-T versus placebo as treatment for metastatic CRPC.[74,75] Both trials showed an overall survival advantage of approximately 4 months. There was no difference in median time to progression and most patients had never received chemotherapy. These findings led to the FDA approval of sipuleucel-T in April 2010 for the treatment of asymptomatic or minimally symptomatic CRPC. For this reason, it is often used prior to docetaxel in patients with minimal or no symptoms.

Second-line therapies for CRPC include chemotherapeutics and agents that target the androgen axis. Mitoxantrone quickly fell out of favor after the FDA approved cabazitaxel in June 2010 as a second-line treatment of CRPC.[76] Cabazitaxel is a semi-synthetic derivative of docetaxel and is similar to docetaxel in that it also inhibits mitosis by stabilizing microtubules. De Bono et al performed an open-label randomized phase III trial in 755 men with CPRC who progressed during or after docetaxel treatment and were either given mitoxantrone or cabazitaxel therapy plus prednisone.[77] The median survival benefit of cabazitaxel over mitoxantrone was 2.4 months, with improvement in progression-free survival in the cabazitaxel arm as well. The most common adverse events were neutropenia and diarrhea in the cabazitaxel arm.

Because our understanding of the continued importance of the androgen axis despite castration has evolved, new agents that target this axis have been developed and are available for use. Although the testicles produce 90% to 95% of the testosterone in the male body, there are other sources of androgens within the body that can fuel prostate cancer, including adrenal glands and even the prostate cancer itself.[78] There are several treatments that target androgen synthesis, including aminoglutethimide, ketoconazole, and newly FDA approved abiraterone acetate. Aminoglutethimide inhibits the conversion of cholesterol to pregnenolone, which not only blocks the production of androgens, but cortisol and aldosterone as well, causing a medically induced total adrenalectomy.[79] Patients treated with aminoglutethimide thus require supplementation of these compounds, and this agent has fallen out of favor due to its significant side effects.[80] Ketoconazole, originally used as an antifungal, inhibits the CYP 17 enzyme and downstream androgen synthesis. It has been mainly used as palliative or emergency therapy for those who have failed first-line androgen-ablation or have pending spinal cord compression, due to its nonspecific nature and side effects.[81,82] Since it also inhibits cortisol production, hydrocortisone supplementation must be given in conjunction with this treatment.

Abiraterone acetate is a selective inhibitor of 17α-hydroxylase and C17,20-lyase, resulting in decreased synthesis of androgens and excess synthesis of aldosterone and its precursors.[83,84] Main side effects include hypertension, hypokalemia, and lower extremity edema. A phase III randomized, controlled trial assessing abiraterone use in metastatic CRPC patients who had failed docetaxel therapy showed a median overall survival improvement of 14.8 months, versus 10.9 months in the placebo arm.[85] The secondary end points of time to PSA progression, progression-free survival, and PSA response rate favored the abiraterone group as well. This study led to FDA approval of abiraterone in April 2011 for men with metastatic CRPC who failed initial chemotherapy. Because of the strong effects of abiraterone observed in the post-chemotherapy population, Ryan et al performed a double-blind, randomized, placebo-controlled trial to evaluate its effects on a pretreatment cohort.[86] This study randomly assigned 1088 men with CRPC to receive abiraterone plus prednisone or placebo plus prednisone prior to any chemotherapy. Coprimary endpoints were radiographic progression-free survival and overall survival. The study was unblinded after an interim analysis was performed after 43% of the expected deaths had occurred, allowing for cross-over. The study showed a radiographic progression-free survival of 16.5 months in the treatment arm versus 8.3 months in the placebo arm. There was also improved overall survival, although this was not statistically significant. These findings led to the FDA approval of abiraterone for treatment of metastatic CRPC in patients without prior chemotherapy.

In addition to agents that target the androgen synthesis axis, newer agents that target and block the androgen receptor pathway have been developed. Enzalutamide, a more potent analogue of bicalutamide, inhibits androgen receptor function as well by blocking nuclear translocation, DNA binding, and co-activator recruitment of the androgen receptor.[87] Promising results from early phase trials conducted by the Prostate Cancer Clinical Trials Consortium led to the phase III double-blind, placebo-controlled trial that stratified 1199 men with CRPC after chemotherapy in a 2:1 ratio to receive enzalutamide or placebo.[88] The primary end point was overall survival. The median overall survival in the treatment arm was 18.4 months versus 13.6 months in the placebo arm. The advantage of enzalutamide was also seen with all secondary end points, which included the soft tissue response rate, time to PSA progression, radiographic progression-free survival, time to first SRE, and proportion of patients with a reduction in PSA greater than 50%. This led to the FDA approval of this medication in August 2012 for patients with CRPC after failing chemotherapy. Treatment options for metastatic CRPC are summarized in **Table 2**.

CASE PRESENTATION CONTINUED

Due to his advancing disease, the patient is counseled regarding all of the options available. He elects to proceed with sipuleucel-T therapy. He begins the immunotherapy and tolerates it well, only complaining of mild chills. Leuprolide is continued during this time. He continues to receive calcium and vitamin D supplementation and to perform weight-bearing exercises, and he is also started on denosumab for the prevention of SREs from his bone metastases. After immunotherapy, his bone metastases remain stable, but he develops new metastasis to the liver and bowel mesentery. His PSA level begins to rise again, to 44.8 ng/mL and then to 106 ng/mL. Due to these progressions, he is started on docetaxel and prednisone. His PSA decreases to 71.8 ng/mL and then to 13.3 ng/mL. During this time he continues to receive leuprolide. Bone scan and CT show stable disease. He denies bone pain and his weight loss has tapered off. Next available therapies for future progression after chemotherapy will include abiraterone acetate, enzalutamide, and cabazitaxel.

- **As this patient's disease progresses, what additional therapies could be offered?**

Table 2. Treatment Options for Metastatic Castrate-Resistant Prostate Cancer (CRPC)

Drug	Type of Drug	Indication	Side Effects	Median Overall Survival Benefit
Docetaxel	Chemotherapy agent	First line for CRPC	Fluid retention, sensory dysfunction, pulmonary events, neutropenia, stomatitis	2.5 months
Sipuleucel-T	Immunotherapy agent	First line for nonsymptomatic CRPC	Chills, fever, headache, nausea, cerebrovascular events (not statistically significant)	4.1 months
Cabazitaxel	Chemotherapy agent	Second line	Neutropenia, diarrhea	2.4 months
Mitoxantrone	Chemotherapy agent	Second line for symptomatic CRPC	Neutropenia, heart failure	0 months
Abiraterone	17α-hydroxylase, C17, 20-lyase inhibitor	First/second line	Hypertension, hypokalemia, lower-extremity edema, increased aldosterone (must give with prednisone)	3.9 months (in chemotherapy-naïve patients)
Enzalutamide	Antiandrogen, multiple modalities	Second line	Seizures, fatigue, diarrhea, hot flashes	4.8 months
Radium-223	Radiopharmaceutical	Second line	Cytopenias, nausea, vomiting, diarrhea, peripheral edema, infertility	2.8 months

ADDITIONAL TREATMENTS

Supportive and palliative therapy for patients who do not respond to first- and second-line treatments has been limited, although the recent availability of so many additional therapies has extended overall survival and delayed progression to this final stage. Supportive treatments rely on bisphosphonates or a RANKL inhibitor to prevent bone events such as fracture, radiotherapy and steroidogenesis blockade to alleviate bone pain, and chemotherapeutic agents to help alleviate pain due to other sites of metastases. Radiation therapy can be applied via external beam to specific sites or via systemically delivered active radionuclides targeting diffuse metastatic disease. The most common systemic agents include strontium-89 and samarium-153. These agents do not affect survival, but do alleviate pain in up to 70% of patients either partially or completely, and preferentially accumulate within the bone.[89,90] The most important side effect limiting their use is bone marrow suppression. Recently, radium-223, another bone-targeting radioisotope, has been shown to delay the time to first SRE and to provide a survival benefit in a phase III trial.[91] It is an alpha particle emitter and targets bone better than beta emitters such as strontium-89 and samarium-153. The ALSYMPCA trial was the first phase III trial to show a survival benefit from radiopharmaceuticals. It was a randomized, placebo-controlled trial using radium-223 in men with symptomatic bone metastases from CRPC who had either failed or were unfit for docetaxel. Median overall survival was improved from 11.2 months in the control arm to 14 months in the treatment arm.

Another serious side effect of bone metastases is cord compression, which can have devastating consequences if not treated immediately. Dexamethasone is often the initial treatment of choice to improve symptomatic compression. This is followed by radiation or surgery for unstable fractures that continue to cause neurologic deficits.[92–94]

CONCLUSION

The additive combination of new first- and second-line therapies for metastatic CRPC has significantly extended survival for patients such that we are currently rewriting the life span at this stage of the disease. Many newer agents are in development and emerging, which will likely continue to improve the outlook for these patients in the future.

BOARD REVIEW QUESTIONS

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