Strategies to Circumvent Testosterone Surge and Disease Flare in Advanced Prostate Cancer: Emerging Treatment Paradigms

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Abstract

The testosterone surge and disease flare is a feared complication from initiation of gonadotropin-releasing hormone (GnRH) agonist treatment in advanced prostate adenocarcinoma. It is a common practice to start an average 7-day pretreatment regimen with an antiandrogen agent before initiating GnRH agonist therapy, to circumvent disease flare from testosterone surge. However, this might not be the best strategy and can be harmful, especially in patients at high risk of imminent organ damage from minimal testosterone surge. Surgical castration is a simple and cost-effective method that should be considered in these scenarios. But most patients refuse this procedure because of the permanent and psychologic impact of surgery. Novel GnRH antagonists, such as degarelix, and cytochrome P450 17 (CYP17) enzyme inhibitors, such as ketoconazole, achieve castrate-equivalent serum testosterone levels much faster than traditional GnRH agonists without the need for coadministration of antiandrogens. This article reports on 3 cases of impending oncologic emergencies in advanced prostate adenocarcinoma treated promptly with degarelix and ketoconazole without any disease flare related to testosterone surge. In the setting of symptomatic hormone-naïve metastatic prostate cancer, the authors suggest clinical trials using abiraterone, orteronel, and other newer agents that target the CYP17 axis (eg, ketoconazole) for fine-tuning the emergent medical castration methods and avoiding the dangers from the flare phenomenon. (*J Natl Compr Canc Netw* 2015;13:e49–e55)

Despite improvements in therapy for prostate cancer, oncologic emergencies, usually encountered in patients with advanced disease, continue to present challenges to the practicing oncologist. Common presentations include spinal cord compression from bone metastasis and bladder outlet obstruction from an enlarged prostate. Pericardial tamponade from pericardial metastasis is rare and has been reported in advanced prostate cancer.¹ Although the availability of better therapies has made these difficult problems increasingly manageable, prompt recognition and the institution of adequate therapy are essential. Androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists has remained the mainstay of prostate cancer treatment for years. However, GnRH agonists, when used alone in these oncologic emergencies, can cause initial testosterone surge and worsen the symptoms caused by disease flare. The risk of flare is greatly affected by the volume of disease present at the initiation of GnRH therapy and by the site of metastasis.² This article presents 3 cases of impending nerve root compression, spinal cord compression, and cardiac tamponade, demonstrating effective therapeutic approaches to avoid testosterone-related disease flare.

Case Presentations

Case 1

A 45-year-old Caucasian man presented with fatigue, weight loss (30 pounds in 2 months), and back pain, which he had experienced for a few months. The back pain was located between his shoulder blades, radiating to his right arm, and associated with some numbness. MRI of his spine revealed indeterminate lesions in cervical and thoracic vertebrae. He also had extensive cervical and soft tissue signal abnormalities in the inter-

From Roswell Park Cancer Institute, Buffalo, New York.
Submitted June 6, 2014; accepted for publication
December 3, 2014.

Dr. George has disclosed that he has received research funding from GlaxoSmithKline, and is a consultant and advisory board member for AVEO Pharmaceuticals, Inc., sanofi-aventis US LLC, Bayer HealthCare/Algeta, and Novartis. The remaining authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

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spinous region, without cord compression, suggestive of metastatic disease (Figure 1). The lower right cervical nerve roots (C5–7) appeared to be compromised by enhancing foraminal, paraspinal soft tissue. Subsequent CT-guided biopsy of the thoracic vertebral lesion revealed metastatic adenocarcinoma of prostatic origin and his prostate-specific antigen (PSA) level was elevated at 149 ng/mL. His local oncologist started him on bicalutamide (antiandrogen) for 2 weeks followed by a leuprolide (GnRH agonist) injection. A week after initiation of the GnRH agonist, the patient noticed worsening weakness in his right upper extremity associated with increasing numbness. He presented to Roswell Park Cancer Institute for a second opinion, and reported that he was unable to move the ring and little fingers on his right hand. He was immediately started on high-dose ketoconazole (400 mg orally 3 times daily) along with hydrocortisone. One week later, his symptoms were stable. However, weakness persisted in the right upper extremity. A 240-mg loading dose of degarelix (a GnRH antagonist) was then administered subcutaneously. Ketoconazole was discontinued and hydrocortisone was tapered. He received another dose of degarelix (80 mg subcutaneously) 4 weeks later. His motor strength improved in approximately 2 months, at which point he was transitioned to a GnRH agonist.

Case 2

A 75-year-old African American man was initially diagnosed with localized, Gleason grade 7 (3+4) prostatic adenocarcinoma. He underwent radical

prostatectomy, which revealed pT2cN0 disease. He had no extra prostatic extension or seminal vesicle involvement and margins were negative. His PSA level was 10 ng/mL before surgery and decreased to less than 0.01 ng/mL after prostatectomy. After surgery he was lost to follow-up. Seven years later, he presented with 3 weeks of gait unsteadiness associated with back pain and a 15-pound unintentional weight loss. The pain he was experiencing was intermittent in the lower back radiating down to the back of his legs and to the front of his abdomen in a band-like fashion. He denied any bowel or bladder incontinence. On examination, he experienced moderate tenderness to palpation in the lower thoracic spine and his gait was guarded, especially when attempting to walk in a straight line. Otherwise, no gross focal neurologic deficits were noticed. Blood work was unremarkable, except for elevated alkaline phosphatase and PSA levels (9.8 ng/mL). CT scan of the abdomen showed a blastic lesion at the T9 vertebral level with extension to the pedicles and spinous process. Central canal impingement was seen on MRI (Figure 2). Additionally, extension of the tumor into the adjacent left posterior 9th rib at the costovertebral junction was seen. Bone scan (Figure 2) revealed widespread bony metastases, most prominent in the thoracic spine. In view of the impending cord compression and his prior noncompliance, the patient was offered emergent bilateral orchiectomy to attain rapid decline in testosterone levels. However, he refused to undergo surgery. He was given the GnRH antagonist degarelix (240 mg subcutane-

Figure 1 Extensive soft tissue abnormality (arrow) in lower cervical interspinous area, without spinal cord compression, suggestive of metastasis.

Figure 2 (A) Bone scan showing increased activity at the lower (T8–T10) thoracic region. (B) T1-weighted sagittal MRI demonstrating a T9-centered metastatic focus causing some spinal cord compression (arrow).

ously). Subsequently, his pain resolved and his gait improved in 2 days. His PSA level decreased to 0.7 ng/mL and he underwent thoracic laminectomy at the levels of T8, T9, and T10, with removal of an epidural-based tumor in 2 weeks. Pathology revealed adenocarcinoma of prostatic origin, with immunohistochemical staining positive for PSA and PSAP (prostate-specific acid phosphatase). After surgery, he was much more comfortable and able to ambulate and perform activities of daily living independently.

Case 3

A 41-year-old Caucasian male presented with worsening generalized bone pain, fatigue, and weight loss experienced over a few months. CT scan showed diffuse bony metastatic lesions (involving spine, ribs, and appendicular skeleton), lymphadenopathy (mediastinal and retroperitoneal), and moderate pericardial effusion (Figure 3). Workup also revealed an elevated PSA level (9295 ng/mL) and elevated alkaline phosphatase. Subsequent prostate biopsy revealed high-risk adenocarcinoma with a Gleason grade 9 (4+5). He was admitted to the hospital 3 days later, after presenting with worsening bone pain and dyspnea on exertion. He denied bowel or bladder incontinence. On examination, muscle strength was slightly decreased in lower extremities, but no obvious neurologic deficits were noted. He was found to have distended neck veins with prominent jugular venous pulsations. MRI of the spine did not reveal signs of cord compression. However, transthoracic echocardiogram revealed moderate pericardial effusion with hemodynamic signs of early tamponade,

along with echogenic densities within pericardium, consistent with metastatic disease (Figure 4).

In view of early tamponade, he was given ketoconazole (400 mg 3 times daily) along with hydrocortisone. The next day, he was taken to the operating room to evaluate the possibility of pericardial drain placement, and bedside cardiac ultrasound revealed very minimal pericardial fluid, precluding the need for drainage. Additionally, within 24 hours of ketoconazole initiation, his testosterone levels dropped to 60 ng/dL and PSA level decreased by approximately 50% (5304 ng/mL). Subsequently, his pain and breathing improved and he was discharged uneventfully. He was later transitioned to GnRH agonist without any disease flare. Currently, he is alive 3 years after the initial presentation and has evolved through different treatments.

Discussion

The principle of ADT as a treatment for advanced prostatic adenocarcinoma was initially described in 1941.³ Authors demonstrated that lowering testosterone through surgical castration or injection of estrogens induces a major regression of prostate adenocarcinoma and rapid relief of symptoms from metastatic disease. A few years later, the discovery of the GnRH receptor and synthesis of the first GnRH analog established ADT as the key systemic treatment against prostate adenocarcinoma.⁴ In the modern era, clinicians are still relying on this principle in the first-line treatment of metastatic hormone-sensitive prostate cancer.

Figure 3 CT scan revealing moderate pericardial effusion (arrow).

Figure 4 Transthoracic echocardiogram showing circumferential pericardial effusion (star) and echogenic density attached to visceral pericardium (arrow), consistent with metastatic disease.

ADT can be accomplished either surgically (bilateral orchiectomy) or medically (using GnRH agonist or antagonist; Table 1). Both methods are equally effective and achieve a reduction in PSA levels, overall tumor burden, and complications, such as pathologic fractures, obstructive uropathy, or spinal cord compression.⁵ Although surgical orchiectomy has fallen out of favor in Europe and North America, mostly because of concerns about the permanent and psychologic impact of surgery,⁶ it remains the initial preferred treatment in many parts of the world and is also viewed as a treatment option should an immediate decrease in testosterone be warranted. Castrate levels of testosterone are normally achieved in 3 to 12 hours (mean, 8.6 hours) with bilateral orchiectomy.^{3,7} It is a simple procedure that could be performed under local anaesthesia. It is very cost-effective and patients do not need to be on lifelong GnRH agonist therapy afterwards. Surgical castration may actually be more appealing in patients whose adherence to medical treatment is poor (such as in Case 2).

Medical castration relies on the modulation of the hypothalamic-pituitary axis through the use of GnRH agonists. Synthetic GnRH analogs are preferred over natural-occurring molecules for their increased affinity for the GnRH receptor. GnRH release from the hypothalamus stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH then stimulates Leydig cells in the testes to secrete testosterone. Release of LH is in turn controlled by GnRH secretion from the hypothalamus, which normally occurs in a regular, pulsatile manner. GnRH agonists override this pulsatile control of the pituitary by providing continuous stimulation, which eventually leads to downregulation of pituitary GnRH receptors, a reduction in LH production, and therefore a sup-

pression of testosterone levels. However, the use of a GnRH receptor agonist initially causes stimulation of the entire axis, resulting in a surge of testosterone.

The initial transitory testosterone surge is the cause of what has been termed the *flare phenomenon*. This surge begins approximately 2 or 3 days after the initial injection of GnRH agonist and lasts through approximately the first week of therapy.² Median serum testosterone levels can increase 2-fold or more above baseline during this period.⁸ Rapid increase in tumor burden can occur with the testosterone surge and is dangerous in scenarios of impending spinal cord compression from bone metastasis and bladder outlet obstruction from an enlarged prostate. Sudden deaths from disease flare also have been reported in the literature.⁹

Wide variation exists in the reported frequency of flare responses (4%–63%) from luteinizing hormone–releasing hormone (LHRH) analogs during the initial treatment of patients with severe metastatic disease,² mainly because of the confusion about biochemical versus clinical flare responses. However, Kuhn et al,¹⁰ who clearly distinguished biochemical from clinical flare reactions, reported a high frequency of 63%. Furthermore, patients at risk for clinical flare are mostly those with widespread symptomatic metastatic disease, rather than those with minimal metastasis or PSA progression only.

It is a common practice to give antiandrogens like bicalutamide, either concurrently or preceding GnRH agonists, and be continued in combination for at least 7 days to prevent a clinically significant flare from testosterone surge.^{10–12} However, this strategy is not always effective. Oh et al¹³ analyzed 1566 patients from Veterans Affairs hospitals with metastatic prostate cancer and showed that antiandrogen therapy given before GnRH agonists was not associated with differences in fractures, spinal cord compression, or bladder outlet obstruction. Antiandrogens might decrease the incidence of clinical flares but do not totally eliminate the occurrence of these flares in high-risk patients (and they do not result in lower testosterone levels).² These agents might not be able to block all of the androgen receptors effectively, especially in cases with bulky metastatic disease associated with a high risk of imminent organ damage from minimal testosterone surge.

This is clearly illustrated in Case 1, in which the patient presented with upper extremity neurologic deficits, secondary to metastatic disease involving

Table 1 Pharmacodynamics of Various ADT Modalities		
ADT Strategy	Time to Attain Castrate Level Testosterone	Risk of Initial Testosterone Surge
GnRH analogs	2–4 wk ^{10,16}	Yes
Degarelix	3 d ¹⁶	No
Ketoconazole	24 h ^{25,26}	No
Surgical castration	3–12 h ^{3,7}	No

Abbreviations: ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone.

the brachial plexus. His symptoms worsened with the antiandrogen/GnRH agonist strategy. He was then treated with the alternative strategy (ketoconazole/degarelix) to achieve rapid castration. However, it took almost 2 to 3 months for him to recover. Although his motor strength improved, it never returned to baseline, suggesting some amount of irreversible damage to the nerve plexus occurred, with the initiation of GnRH analog causing testosterone surge and subsequent disease flare.

Unlike GnRH agonists that initially stimulate GnRH receptors before leading to hypogonadism, GnRH antagonists rapidly and directly inhibit the release of androgens. Therefore, no flare is associated with these agents and no coadministration of antiandrogen is necessary. Abarelix was the first GnRH antagonist available clinically for prostate cancer treatment. However, it was withdrawn from the US market because of concerns about immediate systemic allergic reactions from histamine release.¹⁴ Degarelix was a third-generation GnRH antagonist that was synthetically modified with a view toward reducing this histamine-releasing activity. It was the first GnRH antagonist approved by the FDA in 2008.^{14,15} The pivotal trial (CS21 trial) that led to its approval was an open-label study that randomized 610 patients¹⁶ to 1 of the 3 regimens: monthly 7.5-mg leuprolide or to 1 of 2 degarelix regimens (a starting loading dose of 240 mg degarelix followed by monthly maintenance doses of 80 or 160 mg). Patients in the leuprolide group could receive bicalutamide flare protection at the discretion of the investigator. In this trial, 144 (81%) patients in the leuprolide group experienced a testosterone surge, including 17 of the 23 patients (74%) who received concomitant bicalutamide. None of the patients in the degarelix arms (240/80-mg and 240/160-mg arms) experienced a testosterone surge. Both degarelix and leuprolide achieved the same level of testosterone suppression; 96% of patients receiving degarelix had a testosterone level of 50 ng/dL or lower within 3 days. This novel GnRH antagonist can achieve castrate-equivalent serum testosterone levels (defined as a serum testosterone level ≤ 50 ng/dL) in 3 days versus 2 to 4 weeks with GnRH agonists.^{10,16} In line with the testosterone results, PSA levels also declined more rapidly in the degarelix arms at days 14 and 28.¹⁶

The rapid reductions in testosterone and PSA levels with degarelix suggest that it might be particu-

larly appropriate for patients requiring fast symptom relief (either from primary disease or metastasis) or volume reduction (similar to described cases). Anderson et al¹⁷ from Europe initiated a 12-week phase IIb study in men with predominantly locally advanced prostate cancer and highly symptomatic (lower urinary tract symptoms [LUTS]) disease, comparing degarelix (240/80) with goserelin plus bicalutamide (G/B). The primary end point was change in International Prostate Symptom Score (IPSS) at week 12 compared with baseline. This study was stopped early because of recruitment difficulties, and only 40 patients were treated. Despite this, degarelix was non-inferior to G/B for the IPSS at week 12 and superior in the per-protocol analysis ($P=.04$). Furthermore, degarelix was associated with better improvements in prostate volume and quality of life. Axcrone et al¹⁸ from Norway conducted a similar study in 182 patients with LUTS from locally advanced prostate cancer. Patients were randomized to monthly degarelix (240/80 mg) or G/B for 12 weeks. Reduction of total prostate volume (TPV; measured monthly via transrectal ultrasonogram) was the primary end point and was not different between both arms at week 12, meeting the predefined noninferiority criterion. However, degarelix showed superiority in LUTS relief in symptomatic patients, highlighting its action on extrapituitary GnRH receptors in the bladder and/or prostate. Mason et al¹⁹ showed similar noninferiority of degarelix (compared with G/B) in prostate shrinkage but more pronounced LUTS relief in the neoadjuvant setting before local radiation. These studies underscore the superiority of degarelix in controlling symptoms from locally advanced prostate cancer.

CYP17 inhibitors such as ketoconazole (antifungal agent) block the synthesis of androgens by both gonads and adrenal gland through inhibition of the enzyme 17, 20-lyase.^{20–22} It also has a direct cytotoxic effect on prostatic cancer cells in vitro.²³ High-dose ketoconazole (400 mg administered orally every 8 hours) is studied in prostate cancer and has been shown to reduce bone pain, need for analgesic use, and serum prostatic acid phosphatase levels.²⁴ It has also been shown to cause a decline in serum testosterone level within 30 minutes, produce castrate-equivalent serum testosterone levels within 24 hours of initiation, and a 90% reduction in testosterone level by 48 hours.^{25–27} It is often given in

combination with oral hydrocortisone to prevent Addisonian crisis. However, it is not FDA approved for prostate cancer, because safety and effectiveness have not been established. The most common side effects with prolonged use of high-dose ketoconazole include nausea, vomiting, liver toxicity, skin reactions, and a potential risk of adrenal suppression.^{28–30}

Given the prompt and efficient antiandrogenic properties of ketoconazole, it has been used successfully in cases of metastatic prostatic carcinoma with impending neurologic injury and in patients with acute renal failure caused by bilateral ureteral obstruction from advanced prostatic carcinoma.^{31,32} The terminal half-life elimination for ketoconazole is 8 hours and its inhibitory effect is completely reversible. Testosterone levels and adrenal hormone levels return to normal within 24 hours after cessation of this drug.^{33,34} Therefore, if loading degarelix (240 mg) is also given with ketoconazole in these clinical situations, ketoconazole can be stopped in 3 to 4 days, because degarelix will maintain the castrate-level testosterone by 3 days (of note, degarelix half-life with loading dose is approximately 53 days). The current model that the authors use for emergent medical castration is a loading dose of 240 mg subcutaneous degarelix along with oral ketoconazole at 400 mg 3 times a day (hydrocortisone at 20 mg in the morning and 10 mg in the evening is given to prevent adrenal insufficiency). Ketoconazole can be discontinued within 3 to 4 days (and long-term side effects can be avoided) if concurrent loading degarelix is injected on day 1. The hydrocortisone can usually be discontinued without any adrenal complications. If there are signs of adrenal insufficiency, hydrocortisone taper can be considered.

Oral steroidal progestogens with additional antiandrogenic and antigonadotropic properties such as cyproterone acetate (CPA)^{35,36} and chlormadinone acetate (CMA)^{35,37} were also studied to evaluate their effect on testosterone suppression. Appu et al³⁸ showed that CPA administration before GnRH agonist injection achieved a castrate level of testosterone in 1 week; however, it did not eliminate the surge in serum testosterone when a GnRH agonist was administered.³⁸ A Japanese study showed that CMA was capable of preventing testosterone flare in advanced prostate cancer.³⁹

Conclusions

Testosterone surge and disease flare occur at varied frequency when LHRH agonists are used for the initial treatment of symptomatic patients with widely metastatic prostate adenocarcinoma, depending on the volume of disease. These side effects are often dangerous, and sudden deaths have been reported from the clinical flare response. A crucial factor that determines irreversible damage from a potential flare phenomenon could be the metastatic sites of disease, including paraspinal cord lesions, pericardial metastasis with effusion, and the burden of disease. It is of utmost importance to recognize such impending oncologic emergencies and attain rapid medical castration through avoiding flare phenomenon. Surgical castration is a simple, cost-effective procedure that can achieve castrate levels of testosterone in a few hours, and may actually be more appropriate in patients whose adherence to medical treatment is poor. However, this procedure has fallen out of favor in the United States because of psychologic concerns with bilateral orchiectomy. The common paradigm of GnRH agonist treatment preceded by 1 to 2 weeks of antiandrogen should not be encouraged in these situations. Antiandrogens might decrease the incidence of clinical flares but do not totally eliminate occurrence in high-risk patients. The authors currently use high doses of oral ketoconazole for emergent castration and often administer GnRH antagonist (degarelix) loading dose on the first day, to allow for the quick discontinuation of ketoconazole.

The described cases underscore the ease of administering degarelix and ketoconazole and the rapidity of lowering androgen levels without causing testosterone surge, compared with the GnRH agonist/antiandrogen strategy. In the setting of symptomatic hormone-naïve metastatic prostate cancer, the authors suggest clinical trials using abiraterone, orteronel (TAK-700), and other newer agents that target the CYP17 axis (eg, ketoconazole) for fine-tuning the emergent medical castration methods and avoiding the dangers from the flare phenomenon.

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