Ketoconazole as a Secondary Hormonal Intervention in Advanced Prostate Cancer

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Prostate cancer is the most common nonskin cancer in American men, and androgen-deprivation therapy is the cornerstone of treatment for advanced prostate cancer. Unfortunately, the median duration of response to initial androgen deprivation is limited to 18–24 months. After failing primary therapy, many individuals respond to multiple secondary hormonal interventions, such as ketoconazole. A potent adrenolytic agent, ketoconazole is associated with potential hepatotoxicity, adrenal insufficiency, and drug and food interactions. Nurses can greatly impact the course of treatment for patients by being aware of the rationale for the use of secondary hormones, ketoconazole as a hormonal intervention, potential drug interactions, side effects, and management of toxicities.

At a Glance

✦ New therapies beyond hormones are needed to improve outcomes for patients with progressive prostate cancer; however, some patients with castrate levels of testosterone do respond to multiple, successive hormonal manipulations.
✦ Whether to try additional hormonal manipulations or proceed immediately to cytotoxic therapy depends on functional status, comorbidities, disease extent, and symptoms.
✦ Ketoconazole, an adrenolytic agent used as a hormonal therapy for prostate cancer treatment, can be administered safely and effectively. Close monitoring of drug administration, drug interaction, and toxicity assessment by nurses can greatly impact the overall effectiveness of this regimen while minimizing toxicity.

Prostate cancer is the most common male malignancy, excluding skin cancer, among American men and is the second-leading cause of cancer-related death in males. The projected incidence for 2006 is 234,460 new cases, and the projected number of deaths is 27,350 (American Cancer Society, 2006). Prostate cancer ranks third in cancer incidence worldwide and sixth in cancer mortality among men (Parkin, Bray, Ferlay, & Pisani, 2002). However, considerable variability regarding incidence and mortality exists worldwide, with incidence rates as low as 1.08 per 100,000 in China and 5.5 per 100,000 in Japan to as high as 17.9 per 100,000 in the United States (Jemal, Thomas, Murray, & Thun, 2002), where prostate-specific antigen (PSA) screening is used widely. Prostate cancer commonly is viewed as a disease that affects older men; in fact, age 72 is the median at diagnosis (National Cancer Institute, 2005). The disease occurs more frequently in those with a family history as well as in African American men.

Microscopic foci of cancer are evident in most men with increasing age; however, only a small proportion of the slow-growing tumors progress to invasive prostate cancer, and an even smaller number result in premature death (Boyle, Severi, & Giles, 2005). For patients who develop metastases, the disease is incurable by any therapeutic modality currently available (Lauffer & Eisenberger, 2002). The outcome for those patients is bleak because the disease becomes progressive and, for some, eventually fatal (Lauffer & Eisenberger). The mainstay for advanced disease has been androgen-deprivation therapy since the 1940s, when Huggins and Hodges (1941) observed that surgical orchectomy or the administration of estrogen could reduce tumor size, decrease acid phosphatase, and palliate symptoms of disease. Despite response rates to initial androgen-deprivation therapy of 80%–90%, nearly all men experience progression after an average of 18–24 months; therefore, at that point, second-line hormone therapy should be considered (Dawson, 2002).

The aim of this article is to describe the role of secondary hormones, specifically ketoconazole, in the treatment of advanced prostate cancer and to highlight the importance of drug interactions, side effects, and management of toxicities as secondary hormonal therapies.
prostate cancer. The following will be discussed: (a) the role of primary androgen-deprivation therapy in prostate cancer, (b) the use of secondary hormonal interventions in patients who have failed primary androgen-deprivation therapy, (c) ketoconazole as a form of secondary hormonal intervention, and (d) oncology nurses’ role in caring for patients receiving ketoconazole and other forms of secondary hormonal intervention.

**Primary Androgen-Deprivation Therapy**

Testosterone and its metabolites play a critical role in the growth of healthy and cancerous prostate tissue. The enzyme 5α-reductase catalyzes the conversion of testosterone into the more potent androgen dihydrotestosterone, which fuels prostate cancer cell growth and prevents cell death by binding to the androgen receptor located in the nucleus of the prostate cancer cell. Luteinizing hormone-releasing hormone (LHRH) from the hypothalamus stimulates the anterior pituitary to release gonadotropin luteinizing hormone (LH). LH then stimulates the Leydig cells of the testes to secrete testosterone, which is controlled by a feedback loop. The Leydig cells of the testes are the primary source of testosterone and other androgens; whereas the adrenal gland can account for approximately 5%–10% of circulating androgens (Schroeder, 1998), as much as 45% of residual androgens may be present in tumors after orchietomy alone (Labrie et al., 1983). Androgen-deprivation therapy, the standard of treatment for advanced prostate cancer, can be accomplished in a variety of ways, including disruption of the hypothalamic-pituitary-gonadal axis by surgical or medical castration, adrenal suppression, and inhibition of androgen binding to the receptor site. Medical androgen-deprivation therapy generally is achieved by the administration of LHRH agonists or antagonists such as goserelin acetate, leuprolide acetate, or abarelix, either alone or concomitantly with an antiandrogen such as flutamide, bicalutamide, or nilutamide. The combined use of LHRH analogs with an antiandrogen is referred to as a combined androgen blockade. Androgen deprivation can be performed surgically with a bilateral orchietomy; however, many patients prefer medical castration primarily to avoid surgery but also because of equivalent outcomes (e.g., convenience, temporary treatment of intermittent or cycled hormones for six months on and six months off). The rationale for intermittent hormones is to delay resistance and decrease the effects on androgen ablation, but long-term effectiveness is unclear (National Cancer Institute, 2006). Cycling generally continues as long as patients have a clinical response to therapy.

The process of apoptosis or programmed cell death has been associated with the regression of prostate cancer induced by the removal of androgens and estrogens (Tapia-Vieyra & Mas-Oliva, 2001). Monotherapy in the form of orchietomy or LHRH agonists does not block adrenal androgen production; therefore, an antiandrogen frequently is administered in addition to the LHRH agonist (Kelly & Dodd, 2000). Antiandrogens work by blocking the binding of dihydrotestosterone to its receptor. Although the benefits of combined androgen blockade or the addition of an antiandrogen at initiation of hormonal therapy are minimal ("Maximum Androgen Blockade," 2000), the addition of an antiandrogen after initial failure of androgen deprivation can result in declines in PSA and objective tumor responses (Fowler, Pandey, Seaver, & Feliz, 1995; Scher et al., 1997).

**Secondary Hormonal Interventions**

Before the 1990s, patients who developed progressive disease after initial androgen deprivation were considered to have hormone-refractory prostate cancer or androgen-independent disease; however, research has shown that many of these patients respond to a variety of hormonal interventions. The mechanism, although not fully understood, likely is related to multiple factors, including mutations in the androgen receptor (Feldman & Feldman, 2001).

The possibilities for hormonal manipulations initially were addressed when Scher and Kelly (1993) concluded that a trial of flutamide withdrawal is reasonable in asymptomatic men with a rising PSA before commencing more potentially toxic treatments. Their assertion was based on observations of noteworthy PSA declines (i.e., 80% or more in nine patients and 50% or more in one patient) in 10 of 24 patients who had a median duration of response of five months. Originally referred to as flutamide withdrawal, the phenomenon subsequently was deemed antiandrogen withdrawal when similar results were observed with bicalutamide and nilutamide (Dawson, 2002). Antiandrogen withdrawal now is considered a standard of care when patients demonstrate progressive disease (Chaudhary, Rashid, Onitilo, & Bissada, 2005). Potential treatment options for patients who continue to have progressive disease despite antiandrogen withdrawal include observation, secondary hormones, chemotherapies such as docetaxel, and clinical trials (Chaudhary et al.). Secondary hormonal interventions are used when patients progress on androgen-deprivation therapy and include (a) the addition of an antiandrogen for patients treated with monotherapy or an LHRH analog or orchietomy alone, (b) antiandrogen withdrawal for patients treated with a combined androgen blockade, (c) a trial of another type of antiandrogen for individuals who have responded to antiandrogen withdrawal, or (d) the use of adrenolytic agents such as ketoconazole, aminoglutethimide, corticosteroids, and estrogenic compounds. The course of hormonal intervention is dictated by a multitude of factors such as the velocity of PSA elevation and disease progression, patient response to previous hormonal interventions, comorbidities, performance status, and desire for treatment.

Treatment for patients who do or do not respond to initial antiandrogen withdrawal remains controversial; however, some individuals will continue to respond to other hormonal manipulations and secondary hormones (Eastham & Sartor, 1998; Scher, Isaacs, Fuks, & Walsh, 1995; Small & Vogelzang, 1997). Response rates to second- and third-line oral antiandrogens and hormonal interventions vary, but patients can have prolonged PSA responses without significant toxicity. As a result, secondary hormonal interventions generally are considered primarily for patients with little to no tumor burden and relatively few symptoms. Review of the data supports the use of sequential antiandrogens and suggests that patients who respond to a particular antiandrogen are more likely to respond to secondary
Ketoconazole as a Second-Line Hormonal Intervention

After testicular androgen has been suppressed maximally, the possibility remains that nontesticular androgens will continue to provide stimulus for tumor growth. One type of adrenolytic agent, which is a potential form of secondary hormonal intervention, is ketoconazole, but it is considered by many to be the most toxic of the interventions. Nurses can greatly impact patients’ overall course of treatment, compliance with the regimen, and quality of life with thorough assessments, follow-up, interventions, and ongoing education.

Ketoconazole, an imidazole derivative, is well known for its broad-spectrum antifungal profile (Borgers, Van den Bossche, & De Brabander, 1983). It exerts its clinical effect through the inhibition of cytochrome P450 14α-emethylase and is a potent inhibitor of P450-dependent adrenal and testicular androgen. When ketoconazole initially was developed, a subset of men developed painful gynecomastia, which subsequently was found to be a symptom of adrenal and testicular suppression. That observation led to its use in the treatment of advanced prostate cancer. Ketoconazole normally is given at doses of 200 mg per day; however, when given at doses of 1,200 mg per day, the drug can produce castrate levels of testosterone within 24 hours (Scher et al., 1995). The outcome is particularly beneficial for patients who are admitted with spinal cord compromise or disseminated intravascular coagulation because clinical improvement can be achieved rapidly without immediate surgical intervention (Scher et al., 1995).

In a wide-ranging review of 10 trials of second-line therapies in 1993, an overall response rate of 46% was noted in 171 patients treated with ketoconazole (Dawson, 1993). Small, Baron, Fippin, and Apodaca (1997) reported on 50 men with progressive disease after combined androgen blockade and antiandrogen withdrawal who subsequently were treated with ketoconazole and hydrocortisone therapy. Overall, 30 men (62.5%) experienced a PSA decline of more than 50%, whereas 25 (48%) had a decline of more than 80%, with a median duration of response of 3.5 months. A more recent study by Small et al. (2004) evaluated the responses to antiandrogen withdrawal alone or in combination with ketoconazole; objective responses were observed in 27% of patients undergoing ketoconazole treatment in combination with antiandrogen withdrawal as compared to 11% who underwent antiandrogen therapy alone. Although responses to secondary hormonal interventions such as antiandrogen withdrawal or ketoconazole may be minimal, because of the ease of implementation, overall quality-of-life benefits, and the potential for objective responses, secondary hormonal interventions warrant exploration in a population that has limited therapeutic, beneficial, and curative options.

In the oncology setting, ketoconazole generally is prescribed at much higher doses than those used for the treatment of fungal infections. The standard dose in the oncology setting typically is 400 mg every eight hours, but because of potential intolerance and side effects, some clinicians initiate treatment at 200 mg every eight hours. As a result of the inhibitory effect of ketoconazole on the adrenal steroid synthetic pathways, replacement doses of hydrocortisone may be required (Harris, Weinberg, Bok, Kakefuda, & Small, 2002). Replacement doses of 40 mg are started either on initiation of treatment with ketoconazole or after a patient exhibits symptoms of adrenal insufficiency (e.g., fatigue, fever, malaise). Side effects of ketoconazole include nausea and vomiting in as many as half of patients and rash or dry itchy skin in 10%, as well as fatigue, nail dystrophy, asthenia, and gynecomastia (Dawson, 2002). Other side effects are sleepiness, headache, diarrhea, photosensitivity, fever, thrombocytopenia, impotence, oligospermia, and a disulfiram-like reaction to alcohol (Nichols, 2000). More serious, potential side effects are chemical hepatitis, adrenal insufficiency, and drug interactions.

Although the incidence of hepatic dysfunction is low, hepatotoxicity with elevation of liver function tests is a serious side effect of ketoconazole therapy. Nichols (2000) noted that three cases of liver necrosis have been fatal but did not elaborate on details. The drug may accumulate in patients with compromised liver function; therefore, liver function tests and plasma concentration of drugs should be monitored in such patients. Other drugs with potential hepatic metabolism and/or dysfunction should be used with caution.

Sarver, Dalkin, and Ahmann (1997) reported a case of ketoconazole-induced adrenal crisis in a patient with metastatic prostate cancer. In their follow-up literature review, Sarver et al. acknowledged that the case was the only report of adrenal crisis in a patient receiving ketoconazole for prostate cancer. However, reports of adrenal insufficiency exist in patients treated with high-dose ketoconazole for fungal infections (Sarver et al.). Adrenal insufficiency can be rapidly lethal if treatment is delayed. For long-term use, a medical alert bracelet noting adrenal insufficiency is recommended.

Because of ketoconazole’s potent inhibition of P450 cytochromes, the potential exists for many drug interactions and altered therapeutic levels of drug metabolites. Inhibition of certain cytochrome P450 system enzymes in the liver can potentiate the effects of some drugs such as cyclosporine, phenytoin, oral hypoglycemics, oral anticoagulants, methylprednisolone, and sildenafil. Although ketoconazole can cause an increase in plasma blood levels of some drugs, it can decrease therapeutic levels of other drugs such as theophylline and has been associated with life-threatening side effects when used in conjunction with cisapride, which no longer is marketed for sale in the United States (Wysowski & Bacsanyi, 1996). Ketoconazole is contraindicated for use with Tikosyn® (Pfizer Inc., New York, United States (Wysowski & Bacsanyi, 1996). Ketoconazole is contraindicated for use with Tikosyn® (Pfizer Inc., New York, United States (Wysowski & Bacsanyi, 1996).
NY) and triazolam. Other drugs can alter ketoconazole’s absorption (e.g., antacids, histamine blockers, anticholinergics) and increase its metabolism (e.g., rifampin, isoniazid). As a result, ketoconazole should be used with caution to maintain therapeutic safety and provide maximum treatment outcomes, especially when combined with drugs that are metabolized heptatically.

Ketoconazole is administered orally, dissolves in the acidic gastric environment, and is absorbed through the gastric mucosa (Mycek, Harvey, & Champe, 2000). Food, antacids, cimetidine, and rifampin impair absorption, whereas the acidic nature of cola has been shown to enhance absorption (Mycek et al.). Vitamin C administration can increase bioavailability in men with atrophic gastritis (Dawson, 2002). Generally, ketoconazole should be administered to patients with an empty stomach (one hour before or two hours after a meal) with an acidic environment (e.g., orange juice, cola, vitamin C), and buffering medications such as antacids should be avoided (Mycek et al.; Small et al., 1997). For individuals who suffer from gastrointestinal distress, ketoconazole may be taken with food; sometimes a decrease in dosing can lessen gastrointestinal toxicities.

Ketoconazole (for Prostate Patients) (kee-toe-KON-uh-zole)
Also known as Nizoral® [McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA]

Ketoconazole is a drug used to treat fungal infections. It is also used as a second- or third-choice hormonal agent to treat prostate cancer.

The growth of prostate cancer cells is partially dependent on the male sex hormone, testosterone. At higher doses, ketoconazole blocks the production of male hormones in the testicles and the adrenal glands. This can slow the growth of some prostate cancers.

How It Is Given
Orally (by mouth) in pill form. It may be prescribed as one or two tablets taken three times a day. Take ketoconazole as prescribed with orange juice or cola, with or without food, as an acidic environment aids absorption. If you take an antacid, take ketoconazole two hours before or two hours after the antacid.

Side Effects
The following side effects may occur during treatment. Please discuss these with your doctor or nurse.
• You may experience fatigue.
• Nausea, vomiting, or both may occur.
• You may have abnormal liver function test results, which your doctor will discuss with you.
• Abdominal pain may occur.
• Impotence may develop.
• You may develop itching, hives, or both.
• Rarely, diarrhea may occur.

Special Points
• You should not take this medicine if you have ever had an allergic reaction to ketoconazole, miconazole (Monistat® [McNeil-PPC, Inc., Skillman, NJ]), fluconazole (Diflucan® [Pfizer Inc., New York, NY]), voriconazole (Vfend® [Pfizer Inc.]), or itraconazole (Sporanox® [Janssen Pharmaceutica Products, L.P., Titusville, NJ]).
• Tell your doctor or nurse
  – If you are taking warfarin (Coumadin® [Bristol-Myers Squibb, Princeton, NJ]), rifampin, cyclosporine (Sandimmune® [Novartis Pharmaceuticals Corporation, East Hanover, NJ]), phenytoin (Dilantin® [Pfizer Inc.]), prednisone, or triazolam (Halcion® [Pfizer Inc.]).
  – If you have or have had liver disease
  – If you are taking any other medications, including over-the-counter preparations that do not require a prescription, herbal remedies, vitamins, or dietary supplements. Some of these can interfere with ketoconazole.
• You will have a blood test to check your liver enzyme levels when you start taking ketoconazole and then every six to eight weeks while you are taking this drug.
• Check with your doctor before you take any new medications or over-the-counter drugs.
• Avoid drinking alcohol while you are on this medication.

Call Your Doctor or Nurse If You Have
• Difficulty breathing
• Unusual, increased fatigue
• Yellowing of the skin or the white of the eyes (jaundice)
• Dark, tea-colored urine
• Pale stools
• An irregular or fast heartbeat
• Any new or unexpected symptoms
• Any questions or concerns.

Note. This information is selective and does not cover all possible side effects; others may occur. Please report any problems to your doctor.

Figure 1. Ketoconazole Patient Information
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Oncology Nurses’ Role

Oncology nurses play an important role in monitoring patients receiving ketoconazole, educating patients about the role of hormonal interventions, and directing patients’ care to optimize treatment effects and quality of life. Nurses must elicit a comprehensive pretreatment profile addressing any comorbidities, medications, and supplements taken. They should develop appropriate patient education, take initial and ongoing assessments, and manage any adverse reactions. The growth of the consumer and self-help movements has motivated people to become more accountable for their own health and, in turn, has simultaneously prompted nurses and other healthcare professionals to implement patient education and acknowledge its value in patient care. In addition, the research indicates that patient education is efficacious in many different settings and that patients wish to receive education regarding health issues (Coates, 1999). A patient fact card was developed that includes a description of ketoconazole, instructions on administration for optimal absorption, potential side effects, and special points regarding potential drug interactions (see Figure 1). The card includes instructions to call for specific symptoms or any new or unexpected concerns or developments.

Initial and Ongoing Assessments and Education

Before implementing teaching, nurses should perform an initial assessment to acquire important baseline information regarding a patient’s condition, including any pretreatment symptoms, comorbidities, and medications or supplements taken. A thorough, ongoing toxicity assessment must be completed at each clinic visit and between visits if any problems arise. Because ketoconazole has the potential for serious side effects and some drug interactions, oncology nurses play a pivotal role in ensuring optimal quality of life and treatment outcomes for patients by performing thorough assessments, ongoing education, and close monitoring of patient symptoms and concurrent treatments, laboratory values, and toxicities.

Improving the sensitivity of progressive prostate cancer to hormonal manipulations remains an active area of research and likely will continue to grow as more is learned about the androgen receptor and its role in prostate cancer growth. Nurses will continue to optimize patient care and safety by understanding the trends in care, potential toxicities, and appropriate interventions to decrease adverse treatment sequelae. In most cases, ketoconazole can be administered safely with close observation, careful monitoring, and nursing intervention to manage and control symptoms.

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References


