Tolerability of Nonsteroidal Antiandrogens in the Treatment of Advanced Prostate Cancer

DAVID G. MCLEOD

Walter Reed Army Medical Center, Washington, DC; Uniformed Services University of the Health Sciences, Bethesda, Maryland

Key Words. Advanced prostate cancer · Combined androgen blockade · Antiandrogens · Flutamide · Bicalutamide · Nilutamide · Tolerability · Adverse effects

ABSTRACT

This review compares the tolerability profiles of the three currently available nonsteroidal antiandrogens, flutamide, bicalutamide and nilutamide. Pharmacological effects associated with blockade of the androgen receptor are frequent with all three drugs. Gynecomastia and breast pain are seen more frequently during antiandrogen monotherapy than during combination with medical or surgical castration or castration alone, and the reverse is true for hot flashes, which are a side effect of castration. Gastrointestinal symptoms are also common to all three drugs, but diarrhea occurs more frequently in flutamide studies than in bicalutamide or nilutamide studies. Hepatotoxicity has been seen with all three antiandrogens, but acute, reversible hepatitis and fatal fulminant hepatitis have also been reported with both nilutamide and flutamide. All three drugs have been associated with asymptomatic elevations in aminotransferases and may reduce hemoglobin levels. Adverse events that have been reported with nilutamide include interstitial pneumonitis, delayed adaptation to darkness after exposure to bright light and alcohol intolerance. To date, bicalutamide appears to have some advantage over flutamide and nilutamide in terms of tolerability.

The Oncologist 1997;2:18-27

INTRODUCTION

Combined androgen blockade (CAB) is the combination of surgical or medical castration with a drug which has been developed to provide blockade of the androgens at the tumor site (antiandrogen) in the treatment of prostate cancer [1]. One of the first antiandrogens to be used in clinical practice as a component of CAB was the steroidal antiandrogen cyproterone acetate. The steroidal structure probably accounts for the high propensity of cardiovascular side effects [2] and fluid retention [3]. These adverse effects have limited its utility in prostate cancer, and antiandrogens with a nonsteroidal structure appear to be better tolerated. The first of these to be introduced was flutamide (Eulexin™, Schering-Plough International), whose short half-life of 6-8 hours mandates a three-times-a-day dosing regimen. The recently introduced compounds nilutamide (Anandron™, Roussell) and bicalutamide (Casodex™, Zeneca Limited) have longer half-lives of two and seven days, respectively, which allow once-daily dosing.

The efficacy of CAB is still under investigation. Although some studies [4, 5] have shown significant survival benefit of flutamide over placebo when given as part of CAB, other studies could not confirm this [6-11]. However, there is heterogeneity in trial methodology and, in most of the studies that failed to show significant benefit, the statistical power was not sufficient to show a difference [12]. One of two pivotal trials with nilutamide showed benefit in terms of time to progression [13] and survival after long-term follow-up [14], while the other did not [15]. Furthermore, a meta-analysis of seven nilutamide trials, including the two pivotal trials, also concluded that CAB with nilutamide has advantages over castration alone with respect to progression-free survival [16] and overall survival after long-term follow-up [17]. A meta-analysis of 25 randomized trials comparing CAB (castration plus flutamide, nilutamide or cyproterone acetate) with castration failed to confirm a survival benefit for CAB [18]. The methodology of this analysis has been challenged, and a subsequent sensitivity analysis of randomized trials has highlighted a two-year survival benefit of CAB for published studies using nonsteroidal antiandrogens but no advantage for CAB in several smaller studies [19]. As part of CAB, bicalutamide has been demonstrated to be at least equivalent to flutamide with regard to time-to-treatment failure, time to progression,
McLeod 19

and survival, after a median of 95 weeks follow-up [20, 21]. This is the only trial reported to date that compares two antiandrogens in a double-blind manner. A large intergroup study of orchiectomy plus placebo versus orchiectomy plus flutamide is expected to provide the answer on the benefits of CAB utilizing orchiectomy and flutamide. Initiated by the National Cancer Institute in 1989 and closed in 1994, this study (NCI INT-0105) has the statistical power to detect a 25% improvement in the median survival time achieved with orchiectomy.

Despite the ongoing discussions, CAB is being used by many clinicians in the management of advanced prostate cancer. With several antiandrogens now available, there is the option of choosing the drug to derive the maximum benefit from CAB with minimum side effects. This review seeks to aid that choice by addressing the common side effects of the nonsteroidal antiandrogens and highlighting differences in their tolerability profiles.

REPORTING OF TOLERABILITY

In order to establish the tolerability profile of a drug, it is essential that adverse events are reported during clinical trials. Most protocols now define an adverse event as any medical condition (including laboratory assessments) that emerges or worsens during the study, regardless of whether this is found by the investigator as part of the medical examination or is reported by the patient. However, even within this standardized definition, methods of eliciting adverse event data vary among individual trials and trialists. For example, reporting rates are much higher when patients are asked, “Have you suffered from X, Y or Z?” than when they are asked, “Has anything bothered you since your last visit?” or are not questioned at all.

More importantly, the reporting of adverse event data can be biased by the method of assessment. The most objective assessment, which is required by most regulatory authorities, is one in which there is no attempt to assign causality; hence all adverse events are reported, irrespective of their relationship to the study medication. This is the method used in the recent trial of bicalutamide versus flutamide [22]. The practice of assigning causality may lead to biased reporting of adverse events, particularly when done by a third party such as the trial sponsor. In most trials, this bias does not happen and causality is assessed only by the investigator. Even so, different investigators may make different decisions when faced with the same data, and in doing so may introduce a measure of subjective bias. The most widely quoted antiandrogen trial, that of a luteinizing hormone-releasing hormone-A (LHRH-A) with or without flutamide [4], reported only those adverse events that were considered treatment-related.

Tolerability reporting in publications may comprise all adverse events, only treatment-related adverse events, or only events requiring withdrawal of study medication. Sometimes it may not even be possible to determine which method of assessment was used. Literature comparisons of tolerability of different drugs are therefore fraught with difficulty. For this reason, no attempt has been made in this review to pool any of the data from different studies in order to arrive at a mean incidence for adverse events. Instead, ranges of incidences that reflect the differing methodologies have been quoted.

TOLERABILITY OF ANTIANDROGENS

Pharmacological Events

The most common side effects observed in clinical practice with nonsteroidal antiandrogens such as flutamide, bicalutamide and nilutamide are the pharmacological effects of the antiandrogen class, that is, those associated with blockade of the androgen receptor. The large variations in the reported incidences of these effects (Table 1) are probably a result of the different methods of data collection; patients were questioned about the occurrence of hot flashes and breast symptoms in

<table>
<thead>
<tr>
<th>Table 1. Pharmacological adverse events of nonsteroidal antiandrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
</tr>
<tr>
<td>Breast pain</td>
</tr>
<tr>
<td>Combination therapy</td>
</tr>
<tr>
<td>Breast pain</td>
</tr>
</tbody>
</table>
some studies (notably with bicalutamide), while in others only troublesome events were reported. However, there do not appear to be any clinically relevant differences between the three non-steroidal antiandrogens with respect to the severity of pharmacological adverse events.

Gynecomastia and breast pain are seen more frequently during antiandrogen monotherapy than during CAB or castration alone. Hot flashes are a side effect of castration, but are seen most often with medical castration using LHRH-A. For example, pooled data from bicalutamide monotherapy studies show that breast pain was reported in 36% of patients taking 50 mg and 39% of patients taking 150 mg. This compares with only 4% of patients on bicalutamide plus LHRH-A and 2% of patients with castration alone [46]. The figures for hot flashes were 9% for 50 mg monotherapy, 12% for 150 mg monotherapy, 49% for bicalutamide plus LHRH-A, and 43% for castration alone [22, 46]. The comparability of the findings for bicalutamide plus LHRH-A and LHRH-A alone indicates that in combination therapy the pharmacological adverse event profile is dominated by that of the LHRH-A. This finding holds true for all the nonsteroidal antiandrogens. The data also show that for pharmacological events, bicalutamide is not associated with a dose-related increase over the range of dosages from 50-150 mg [46].

In the only double-blind, comparative study of two antiandrogens reported to date, that of flutamide plus LHRH-A versus bicalutamide plus LHRH-A, treatment-related pharmacological adverse events were similar in the two groups (gynecomastia 6% versus 5%; hot flushes 49% versus 50%, respectively) [22].

Pharmacological adverse events seldom require withdrawal of therapy, although severe gynecomastia has been reported in 2% of 599 UK patients in a post-marketing surveillance study of flutamide, the first antiandrogen to be introduced [47].

Non-Pharmacological Events

The non-pharmacological adverse events of the non-steroidal antiandrogens are generally specific to the individual compounds and, unlike the pharmacological adverse events, their incidences are not influenced by castration per se. However, as the tolerability profile of the drugs used to bring about medical castration may influence the tolerability of CAB, monotherapy and combined therapy regimens with antiandrogens have generally been treated separately for the purposes of this review.

Gastrointestinal Events

Adverse events affecting the gastrointestinal (GI) system are reported with all three non-steroidal antiandrogens, but there are differences between the drugs with respect to the nature, frequency, and severity of such events.

Nausea, Vomiting and Abdominal Discomfort

In monotherapy studies, nausea, vomiting and abdominal discomfort appear to be more common with nilutamide (up to 65%) [32, 33] than with either flutamide (5%-6%) [24, 35, 39] or bicalutamide (6%) [26, 28], but this observation may be influenced by the much lower patient numbers in the nilutamide studies.

In combination studies of nilutamide plus surgical castration [13, 44, 47] the 3%-13% incidence of these events is comparable with the 4%-20% incidence reported with combinations of flutamide plus medical castration [4, 6, 7, 10]. The incidences of nausea and general GI problems were also similar in both groups in a direct comparison of nilutamide plus surgical castration versus bicalutamide 150 mg monotherapy (5% versus 3% and 8% versus 7%, respectively) [31].

In comparative studies, all the nonsteroidal antiandrogens, whether used as monotherapy or part of CAB, generally give rise to slightly more nausea, vomiting, and GI distress than castration alone [6, 7, 10, 13, 29, 30, 44, 47].

In the double-blind comparison of flutamide versus bicalutamide, each in combination with an LHRH-A [22], nausea was reported, regardless of causality, in over 10% of patients in both groups and considered related to therapy in 7% and 8% of patients, respectively [46].

Diarrhea

Diarrhea is more common and occasionally more severe with flutamide than with either bicalutamide or nilutamide, often necessitating dose reduction or occasional withdrawal. Incidences of 10%-20%, leading to discontinuation of therapy in 5%-20% of patients, are not uncommon in open-label, monotherapy studies employing a daily dosage of 750 mg flutamide for advanced prostate cancer [24, 42, 48]. In a post-marketing surveillance study involving 599 UK patients, the majority of whom received flutamide monotherapy, diarrhea occurred in 58 (10%) patients and required withdrawal in 30 (5%) [49]. Similarly, in a placebo-controlled, monotherapy, dose-finding study in 372 patients with benign prostatic hyperplasia (BPH), diarrhea occurred with a significantly higher incidence in all flutamide dose groups (29%-34%) compared with placebo (14%). At the dosage commonly used in patients with advanced prostate cancer (250 mg TID), diarrhea occurred in 29% of patients treated with flutamide for BPH and was severe enough to warrant discontinuation in 17% [35].

In large studies comparing flutamide plus LHRH-A with LHRH-A alone, diarrhea was more common in the flutamide groups [4, 7, 8, 10]. The difference achieved statistical significance in one such double-blind, placebo-controlled study.
(14% versus 5%; \(p < 0.001\)) [4]. Although there is no access to the underlying data, the transcript of the proceedings of the 1988 FDA Advisory Committee Meeting [50] included discussion of data from this trial; the incidence of diarrhea, irrespective of relationship to therapy, was presented as 24% in the flutamide group compared with 11% in the placebo group. The difference between the two reports of the same study illustrates the importance of understanding the reporting methodology. The FDA figures confirm the incidence of diarrhea reported in other flutamide studies [22, 35, 42, 48].

In contrast, diarrhea has been reported in only 2%-5% of patients in bicalutamide monotherapy studies [26-31], which include one high-dose (150 mg) study [31], and in only 2%-4% of patients in nilutamide studies, which include monotherapy and combinations with surgical castration [31, 32, 47]. A higher incidence (10%) was seen when bicalutamide was combined with medical castration, but this was significantly lower (\(p < 0.001\)) than the 24% incidence that occurred with flutamide plus medical castration in this double-blind, comparative study [22]. The figures from this study are for adverse events irrespective of relationship to therapy. These data [20, 46] illustrate the nature of flutamide-induced diarrhea which led to withdrawal of therapy in 6% of flutamide patients compared with 0.5% of bicalutamide patients (Fig. 1). However, in this study, dose modification was not allowed; patients were withdrawn if they could not tolerate their randomized therapy.

Hepatic Toxicity

Laboratory Test Abnormalities

Abnormal liver function tests, in particular elevated transaminases, have been reported with all three nonsteroidal antiandrogens. While some of the abnormal results can undoubtedly be attributed to concomitant medications or underlying disease, an association with the antiandrogens cannot always be ruled out.

Incidences of abnormal liver function test results have been variously reported from 2%-33% in nilutamide groups [13, 32, 33, 45] and from 4%-62% in flutamide groups [5, 7, 9, 11, 34, 38-40, 48] in trials of monotherapy and CAB. In a study of LHRH-A plus flutamide or placebo, elevated amino-transferases were significantly more common in the flutamide group than in the placebo group (12% versus 3%; \(p = 0.01\)) [9]. Furthermore, the transcript of the proceedings of the 1988 FDA Advisory Committee Meeting [50] included discussion of data from the large study comparing flutamide plus LHRH-A with LHRH-A alone [4]. When adverse events irrespective of causality were considered, a marginal treatment effect was detected with regard to hepatic adverse events in the flutamide group compared with the placebo group (16% versus 10%; \(p = 0.05\)).

In the double-blind, comparative study of flutamide plus LHRH-A versus bicalutamide plus LHRH-A, elevated transaminases occurred in slightly more patients in the flutamide group than in the bicalutamide group (10% versus 6%; \(p = 0.07\)). This increased incidence was also seen for patients with greatly elevated (>5× normal) transaminase values (2% versus 0.5%) [22, 46].

Clinical Hepatotoxicity

Clinical hepatotoxicity has also been associated with all three nonsteroidal antiandrogens, but there are differences among the three drugs with respect to the nature and severity of the reported conditions. While hepatic failure has been seen with both flutamide and nilutamide, it has not been attributed to the use of bicalutamide in studies of monotherapy or CAB involving 3,717 men [46]. Five patients exhibited jaundice in which bicalutamide-induced hepatotoxicity could not be ruled out, and jaundice (of unknown origin) was thought to contribute to the death of one patient with prostate cancer and chronic renal failure [46].

One case of acute, reversible hepatitis and one case of fatal, fulminant hepatitis have been described in the literature.
for nilutamide [54, 55]. In the latter, the rapidly fatal outcome may have been promoted by phenobarbital, which was administered after the appearance of symptoms and before discontinuation of nilutamide. In addition to these case reports, hepatitis (not defined) has occurred in 2 of 125 (3%) and 1 of 112 (1%) patients in the nilutamide plus castration groups in double-blind comparisons with castration alone and bicalutamide monotherapy, respectively [31, 47]. Flutamide has been described as a potent hepatotoxin in certain patients [56] and clinical hepatotoxicity is well-documented in clinical trial reports [11, 23, 24, 42, 48], individual case reports, and series of case reports [56-65]. Flutamide has a short half-life (six to eight hours for the active metabolite 2-hydroxyflutamide). However, if patients fail to have hepatic enzymes monitored frequently and use of flutamide continues if the enzymes become elevated, (more than twice the upper limits of normal), clinical hepatotoxicity and death can result. Wysowski and Fourcroy reported on liver failure and death in 17 patients [56]. In a large series of 1,091 consecutive patients treated with flutamide in combined therapy, two developed clinical manifestations of liver disease and both had a return to normal liver enzyme levels with discontinuation of flutamide [57]. It is now recommended that baseline liver tests should be drawn and levels determined frequently thereafter for patients taking flutamide. Presenting symptoms in both non-fatal and fatal cases have generally been nausea, vomiting, lethargy, and jaundice. Laboratory abnormalities have included elevated aminotransferases and bilirubin, and, in some cases, prolonged prothrombin times. The predominant features of biopsies in five patients have been cholestasis and hepatocellular necrosis. The dose of flutamide has generally been 750 mg daily, and duration of treatment has ranged from 5 to 300 days. Workups to exclude other possible causes of hepatotoxicity were negative, and, in the non-fatal cases, prompt discontinuation of flutamide resulted in normalization of laboratory tests and resolution of clinical symptoms even when therapy with LHRH-A was continued.

Wysowski and Fourcroy [56] have compared the observed reporting rates for flutamide-induced hepatotoxicity (deaths and hospitalizations) with the expected rates of hospitalization due to liver toxicity in an elderly male population. Between February 1989 and December 1994, the FDA received reports of 20 patients who died and 26 who were hospitalized for hepatotoxicity due to flutamide. This observed rate of approximately 3 per 10,000 treated patients exceeds the expected rate of 2.5 per 100,000 hospitalizations for non-infectious liver injury by 10-fold or more.

Liver function should be monitored periodically in patients on antiandrogens, and therapy should be discontinued if it is persistently abnormal or accompanied by symptoms such as anorexia, nausea, vomiting, fatigue, discolored urine, pruritus, or jaundice.

**Cardiovascular Events**

Patients with advanced prostate cancer are frequently elderly, hence coexistent cardiovascular conditions are quite common in antiandrogen monotherapy and CAB studies.

The nonsteroidal antiandrogens, in contrast to steroidal antiandrogens such as cyproterone acetate, do not appear to be associated with significant clinical cardiovascular toxicity [27, 29, 47]. Although the prescribing information for nilutamide mentions tachycardia and hypertension, while that for bicalutamide mentions angina pectoris and congestive heart failure, the incidences of these events in published studies have not differed significantly from the incidences in the castration-only groups [29, 47].

In an open monotherapy study using 50 mg daily bicalutamide in 267 patients with advanced prostate cancer, the drug did not appear to affect cardiac parameters as assessed by either 12-lead (all patients) or 24-hour (20 patients) ECG recording. Many of the elderly patients in the study had underlying cardiovascular abnormalities that remained unchanged [27]. Indeed, detailed cardiac assessments were made in all the bicalutamide dose-ranging and phase II studies. In contrast to the shortening of the P-R interval and increased heart rate found in preclinical studies with this drug in dogs, these studies in humans revealed no evidence of any such adverse effects [46]. In an analysis of the most frequently reported cardiac adverse events for patients who received bicalutamide in controlled clinical studies (hypertension, heart failure, angina pectoris, myocardial infarction), the incidence was comparable with the prevalence of cardiovascular diseases in the elderly male population [66]. In a comparison of high-dose (150 mg) bicalutamide against nilutamide plus castration, cardiovascular adverse events occurred with a similar frequency in both groups (7% versus 8%) [31].

The prescribing information for flutamide mentions hypertension in 1% of patients and also refers to preclinical studies in beagle dogs in which serious cardiac lesions indicative of chronic injury and repair processes occurred. These included chronic myxomatous degeneration, intramyocardial fibrosis, myocardial acidophilic degeneration, vasculitis and perivascularitis. The doses at which these lesions occurred were associated with levels of the active metabolite 2-hydroxyflutamide that were 1- to 12-fold greater than those observed in humans at therapeutic levels.

While serious cardiac lesions have not been reported in humans, one study comparing flutamide with the estrogen estramustine phosphate found no difference between the two groups with respect to adverse cardiovascular events [67]. In a double-blind comparison of flutamide monotherapy versus
diethylstilbestrol, diethylstilbestrol produced a higher incidence and severity of cardiovascular and thromboembolic complications. However, presumed treatment-related cardiovascular or thromboembolic toxicity was reported in the flutamide group, and was severe, life-threatening, or fatal in 18% [68]. Specifically, hypertension occurred in 13 (38%) patients and was severe or life-threatening in 4 (12%), fatal stroke occurred in 1 (3%) patient, peripheral edema in 9 (26%) and angina pectoris in 2 (6%). The investigators may have been more inclined to assess causality as related to therapy in these double-blind studies because the estrogen comparators are known to be associated with significant cardiovascular toxicity. This might explain the contrast between these findings and those of the majority of published studies of flutamide in which cardiovascular toxicity is seldom among the most commonly reported adverse events. The transcript of the proceedings of the 1988 FDA Advisory Committee Meeting [50] included discussion of data from a large study comparing flutamide plus LHRH-A with LHRH-A alone [4]. When adverse events irrespective of causality were considered, a marginal treatment effect was detected with respect to cardiovascular experiences in the flutamide group compared with the placebo group (12% versus 7%; p = 0.05). In the double-blind comparison of flutamide versus bicalutamide, each in combination with an LHRH-A [22], cardiovascular adverse events occurred in a similar proportion of patients in both groups when all adverse events were considered, irrespective of causality (Table 2).

**Hematological Toxicity**

It is known that androgens stimulate erythropoiesis [69], and decreases in hemoglobin and other red series parameters are therefore to be expected during treatment with antiandrogens. The prescribing information for nilutamide refers to decreases in hemoglobin, hematocrit, and red blood cell count during treatment with nilutamide, and warns that periodic blood counts should be performed during the first three months of therapy. However, in one monotherapy study with nilutamide, both hemoglobin and red blood cell levels increased significantly compared with pretreatment values [32]. Similarly, anemia was slightly less common in the nilutamide-plus-orchiectomy group than in the placebo-plus-orchiectomy group (7% versus 4%) in one comparative study [13]. In bicalutamide monotherapy and combination therapy studies, anemia has occurred in 7%-8% of patients, compared with a 7% incidence seen with castration alone [46]. In the double-blind comparison of flutamide or bicalutamide, each in combination with an LHRH-A, the incidence of anemia in the flutamide group was slightly higher than that in the bicalutamide group (10% versus 7%) [46]. This low incidence contrasts with a higher incidence reported in two uncontrolled studies of flutamide plus LHRH-A when used in addition to radiotherapy [48, 70].

The prescribing information for flutamide lists hemolytic anemia, macrocytic anemia, methemoglobinemia, leukopenia, neutropenia, and thrombocytopenia, but only methemoglobinemia [71, 72], sulphemoglobinemia [73] and neutropenia [74] have been described in the literature. A recent update to the prescribing information for flutamide requires methemoglobin levels to be monitored in patients who are susceptible to aniline toxicity and in patients who smoke. Although all three of the currently available nonsteroidal antiandrogens are structurally related to aniline, amide hydrolysis of bicalutamide does not occur in humans who are not exposed to an aniline derivative of bicalutamide [75].

**Ocular Events**

An adverse event that occurs frequently with nilutamide is delayed adaptation to darkness after exposure to bright light. This has not been reported with either bicalutamide or flutamide. It has been reported with a similar high incidence (11%-50%) in trials of nilutamide monotherapy [32, 33] and combinations of nilutamide plus castration [13, 31, 43-45, 47, 76]. In one study of antiandrogen plus medical or surgical castration in patients with advanced prostate cancer, 20 of the patients were originally randomized to nilutamide, but the occurrence of visual side effects in 70% led to an early change to flutamide and the use of flutamide as the antiandrogen in all subsequent patients [77].

Placebo-controlled trials [13, 47, 76, 78] have demonstrated a greater incidence of delayed light/dark adaptation in the nilutamide groups than in the placebo groups (Fig. 2).

<table>
<thead>
<tr>
<th>Table 2. Incidences of cardiovascular events regardless of causality after a median duration of follow-up of 95 weeks: bicalutamide versus flutamide, each in combination with an LHRH-A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Angina pectoris</td>
</tr>
</tbody>
</table>
In a comparison of nilutamide plus orchiectomy with bicalutamide monotherapy in 230 patients [31], poor light/dark adaptation was reported by 11% of the nilutamide group compared with none of the bicalutamide group. Other (unspecified) visual problems were also more frequent in the nilutamide group (11% versus 0%).

Ophthalmologic studies have confirmed the functional nature of the condition [32, 33, 45, 79]. Visual acuity was unimpaired and there were no anatomical changes of the retina. In one study the delay in adaptation was reported to range from a few seconds to 30 minutes, with most patients reporting a delay of five minutes [76].

An estimated 1%-2% of patients find the visual side effects of nilutamide intolerable [13, 80] and for these patients, and the incalculable number in whom less severe symptoms may nevertheless affect compliance, a change of therapy to either flutamide or bicalutamide which do not affect vision would seem appropriate. Patients who intend to drive should be warned of this possible adverse event when they are prescribed nilutamide.

**Pulmonary Toxicity**

Interstitial pneumonitis in patients treated with nilutamide is well-documented in the literature [81-85], and one case has been reported in a patient treated with high-dose (200 mg) bicalutamide in a clinical trial (H. Scher, personal communication). The incidence of nilutamide-induced interstitial pneumonitis is difficult to estimate, but in a report of a series of eight cases, the authors state that it is second in frequency only to amiodarone-induced pneumonitis which occurs in about 1%-2% of patients, and cite the figure of 1% quoted to them by the manufacturers [81]. In a recent comparison between nilutamide plus castration and bicalutamide monotherapy, interstitial pneumonitis necessitated withdrawal of therapy in 4.5% of the nilutamide group (5/112), compared with no cases of interstitial pneumonitis reported in the bicalutamide group [31].

Presenting symptoms have included dyspnea, fever, and non-productive cough, although in one asymptomatic patient the condition was detected on routine chest radiograph [81]. Where documented, the duration of treatment with nilutamide has ranged from 10 days to 2 years, with the majority of cases occurring in the first three months [81-83, 85]. Investigations have excluded other likely causes such as concomitant medication, infection, or lymphangitic spread from the prostate cancer. Positive rechallenge data are available for one patient [82]. Chest radiographs have shown bilateral pulmonary infiltrates in all cases, radiographic densities of which ranged from minimal to pronounced. Pulmonary function tests have been consistent with a restrictive defect in most cases. On the few occasions where transbronchial biopsy has been performed, this has confirmed the diagnosis of interstitial pneumonitis. Bronchoalveolar lavage has shown lymphocytosis in most cases and increased neutrophils in some [81].

The outcome of this interstitial pneumonitis has usually been favorable, with disappearance of symptoms and an improvement of chest radiograph within days or weeks after discontinuation of nilutamide in most cases, with or without corticosteroids, although complete healing with a return to normal lung volumes and chest radiograph has typically taken from 6 to 12 months. In one patient in whom nilutamide therapy was continued at a reduced dosage, the condition resolved slowly over 12 months. As the severity of the condition appears to be related to the time between onset of dyspnea and consultation [83], chest radiographs should be performed in all patients presenting with unexplained dyspnea of unknown origin or sudden worsening of existing dyspnea following prescription of nilutamide. If interstitial pneumopathy is diagnosed, the drug should be discontinued and appropriate symptomatic therapy initiated.

It may be hypothesized that oxidative stress secondary to nilutamide metabolism is responsible for both the pulmonary and hepatic toxicity of the drug. In rat lung microsomes (and in the liver), nilutamide is reduced by NADPH-cytochrome P450 reductase into a nitro anion free radical which, in the presence of oxygen, undergoes redox cycling, with the generation of reactive oxygen species [86]. Simultaneous hepatic and pulmonary complications have been documented in one patient following two months’ therapy with nilutamide [84].

Dyspnea without evidence of pulmonary infiltration has also been reported in patients on nilutamide, as it has in patients on flutamide and bicalutamide. In a double-blind comparison of nilutamide plus castration against bicalutamide monotherapy, dyspnea was reported in 8% and 1% of patients, respectively [31].
REFERENCES


Alcohol Intolerance

Nilutamide, but not flutamide or bicalutamide, has been associated with alcohol intolerance in 3%-19% of patients in studies involving either monotherapy or CAB [13, 31-33, 43, 44]. The intolerance takes the form of a slight disulfiram-like reaction, with hot flashes and skin rash being the main symptoms [32]. The mechanism by which this reaction occurs is not known. Although alcohol intolerance rarely leads to withdrawal of nilutamide, it may reduce compliance.

Conclusions

Antiandrogen therapy, in combination with medical or surgical castration, is given to enhance survival and to maintain or improve the quality of life of patients with advanced prostate cancer. While many of the side effects of the nonsteroidal antiandrogens are class effects, each drug has specific toxicities which physicians should discuss with patients. Unacceptable side effects of one antiandrogen can often be overcome without loss of efficacy by switching to another drug in the same class.

Bicalutamide appears to have a more favorable tolerability profile than either nilutamide or flutamide on the basis of current evidence. It has not been associated with some of the side effects that are seen with nilutamide or flutamide. However, it must be taken into account that the number of patients exposed to flutamide exceeds that of the other two nonsteroidal antiandrogens.

Antiandrogens are clearly effective in various treatment regimens in prostate cancer care, and clinicians treating patients with advanced prostate cancer should become familiar with this class of drug.
50 Schellhammer P. An antiandrogen with minimal GI toxicity: Case reports from the CASODEX Compassionate Use Study. Contemp Urol 1996;8:31-33.
51 Rosenthal SA, Linstadt DE, Leibenhaut MH et al. Flutamide-associated liver toxicity during treatment with total androgen...