Formulary Forum

NILUTAMIDE:

AN ANTIANDROGEN FOR THE TREATMENT OF PROSTATE CANCER

Ernest J Dole and Mark T Holdsworth

OBJECTIVE: To review the pharmacology, pharmacokinetics, efficacy, and adverse effects of nilutamide and to compare this agent with the currently marketed nonsteroidal antiandrogens (i.e., bicalutamide, flutamide) by critically analyzing the published literature.

DATA SOURCES: MEDLINE (1980–1995) and CANCERLIT (1991–1995) were searched for English-language publications using the terms nilutamide, bicalutamide, and flutamide alone, and either nilutamide or androgen antagonists in combination with prostatic neoplasms.

STUDY SELECTION AND DATA EXTRACTION: All articles with subject matter on nilutamide, bicalutamide, and flutamide were considered for inclusion. For studies published in more than one journal, the first publication was used unless a subsequent publication included additional or follow-up data, in which case the latter publication was cited instead.

DATA SYNTHESIS: Nilutamide was effective in combination with orchiectomy in improving responses in patients with advanced prostate cancer. However, patient survival was not improved in these trials, and improvements in bone pain did not usually result in improved performance status in these patients. The few trials of nilutamide monotherapy or nilutamide in combination with a luteinizing hormone–releasing hormone analog are too small to draw meaningful conclusions regarding its efficacy or its role in the treatment of advanced prostate cancer. No comparative trials of nilutamide with other antiandrogens and no analysis of the impact of nilutamide on patient quality of life are currently available. Nilutamide appears to produce a higher frequency of adverse effects than the other currently marketed nonsteroidal antiandrogens, bicalutamide and flutamide.

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Nilutamide (Nilandron, Hoechst Marion Roussel).

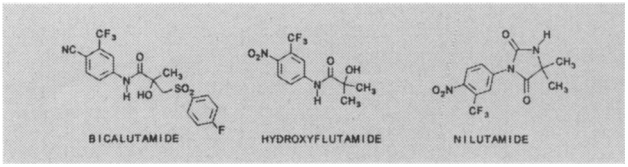

Figure 1. Graphic structures of the nonsteroidal antiandrogens.

CONCLUSIONS: Nilutamide does not appear to represent a major advance in the treatment of advanced prostate cancer and appears to be somewhat inferior to both flutamide and bicalutamide with regard to adverse effects. Nilutamide should not be considered the antiandrogen of choice in the treatment of advanced prostate cancer.

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PROSTATE CANCER IS NOW the most common noncutaneous cancer in American men and is a leading cause of cancer death.[1] It is estimated that in 1996 there will be 317 100 newly diagnosed cases of prostate cancer and 41 400 deaths due to prostate cancer in the US alone. For over 50 years, androgen deprivation has been the main form of treatment in cases of advanced prostate cancer.[2] Antiandrogen therapy is the treatment of choice to palliate the symptoms of advanced prostate cancer; however, this therapy is not curative.[3]

The majority of circulating androgen in males is produced by the testes; therefore, surgical removal or ablation of testicular endocrine function has been the primary mechanism of androgen ablation in prostate cancer. When patients relapse following this intervention, some investigators attempt to induce a second remission by addressing the smaller androgen contribution of the adrenal gland, first with surgical and later with medical adrenalectomy using aminoglutethimide or ketoconazole. Most trials of

adrenalectomy have been conducted in patients whose disease had relapsed, and in this setting, short-lived responses were observed.[4,5] Although relapse of prostate cancer is often attributed to androgen-independent cells,[6,7] an alternative explanation is that androgens of adrenal origin continue to allow growth of prostate cancer. Supporting this theory is the fact that, following gonadal ablation, intracellular concentrations of dihydrotestosterone (DHT) in prostate cancer tissue remain high.[8]

Renewed interest in inhibiting or blocking all sources of androgen, known as total androgen blockade or maximal androgen blockade (MAB), began with the availability of both luteinizing hormone–releasing hormone (LHRH) analogs and various antiandrogen compounds. Administration of LHRH analogs initially stimulates and subsequently suppresses luteinizing hormone (LH) release from the pituitary gland. The latter results in reduction of testicular testosterone production to concentrations found after castration.[9,10] The initial short-lived stimulation of LH may occasionally result in temporary worsening of symptoms (LH flare) in patients with prostate cancer. Two parenteral LHRH analogs (i.e., leuprolide, goserelin) are available for use in the US. Initial therapy with an LHRH analog is equivalent in efficacy to either orchiectomy or diethylstilbestrol (DES) therapy.[9,11]

Both steroidal and nonsteroidal antiandrogen compounds block the action of androgen at the cellular level.[12,13] Combining an antiandrogen compound with an LHRH analog or with one of the standard methods of testicular androgen ablation (e.g., DES, orchiectomy) produces MAB and prevents the initial flare without interfering with adrenal function.[3,14] Flutamide and bicalutamide are the nonsteroidal antiandrogens currently available in the US. Nilutamide was approved for release into the US market by Hoechst Marion Roussel under the brand name Nilandron on November 6, 1996. The main advantage of these agents over the steroidal antiandrogens (e.g., megestrol acetate) is the lack of progestational adverse effects. Given the recent release of nilutamide and the evolving data regarding the efficacy of MAB and antiandrogen monotherapy in the treatment of prostate cancer, it seems prudent that practitioners become cognizant of the current evidence supporting the efficacy of these treatment strategies and the role of this latest nonsteroidal antiandrogen in the treatment of patients with metastatic prostate cancer. This article examines the data supporting the efficacy of nilutamide both in MAB strategies and as monotherapy, and compares its efficacy and toxicity with those achieved with other nonsteroidal antiandrogens in patients with prostate cancer.

Methods for Literature Assessment and Selection

MEDLINE (1980–1995) and CANCERLIT (1991–1995) were used to search the English-language literature under the terms nilutamide, bicalutamide, and flutamide alone, and either nilutamide or androgen antagonists in conjunction with prostatic neoplasms. For clinical efficacy, studies using a double-blind, randomized, controlled design were given highest priority in formulating conclusions, and only studies with comparable treatment groups with regard to previous therapy and disease severity were included. Selection of studies for bicalutamide and flutamide were also based on sound scientific design to allow for appropriate comparisons with nilutamide. When well-controlled trials were not available, open-label trials were used to reach a consensus based on the best available data.

Chemistry

The graphic structures of bicalutamide, hydroxyflutamide (the active metabolite of flutamide), and nilutamide are provided in Figure 1. All three agents are similar in that they possess an aromatic ring with an electron-withdrawing substituent at position-4, a trifluoromethyl group at position-3, and a substituted amide linkage at position-1. These compounds differ in terms of their substituted amide structures.

Pharmacology

The production of androgens is controlled by the hypothalamus and the anterior pituitary gland. A diagram of the relevant pathways involved is provided in Figure 2. The hypothalamus produces LHRH and corticotropin-releasing factor, which stimulate the anterior pituitary to produce LH, follicle-stimulating hormone, and adrenocorticotropic hormone. LH induces the production of testosterone by the Leydig cells of the testes. The production of adrenal androgens (i.e., androstenedione, dehydroepiandrosterone, its sulfate) is stimulated by adrenocorticotropic hormone. Adrenal androgens are converted to testosterone and DHT in the plasma and/or in the prostate gland. As much as 95% of circulating testosterone is re-

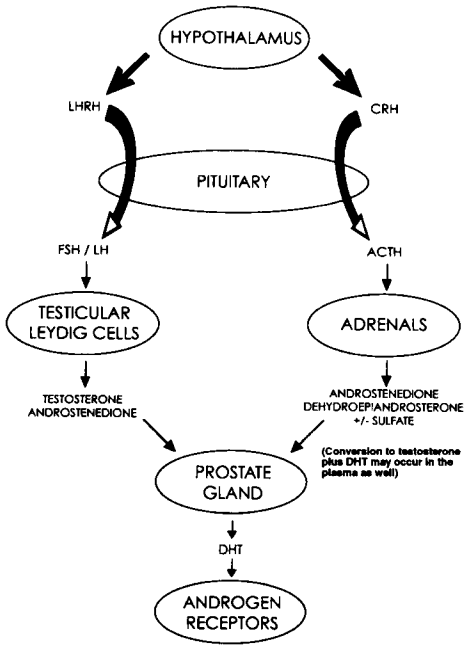

Figure 2. Pathways of androgen synthesis (ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; DHT = dihydrotestosterone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LHRH = luteinizing hormone–releasing hormone).

moved by orchiectomy, LHRH analog, or estrogen (e.g., DES) administration, indicating primary production by the testes. However, the adrenal androgens produce as much as 15–20% of the DHT in the prostate gland,[15] indicating the importance of the adrenal component to androgenic action in prostatic tissue. The adrenal androgen component has been thought to contribute to the continued growth of prostate cancer in men who no longer have a testicular source of androgens. This theory forms the rationale behind MAB.

Antiandrogens counteract the effects of androgens at the target cell level. Steroidal antiandrogens include cyproterone acetate and megestrol acetate. Only the latter agent is currently available in the US; however, it currently does not have approval for use in the treatment of prostate cancer. These agents work by blocking androgen receptors and 5-alpha-reductase activity, and they also possess progesterone-like activity.[16] Steroidal antiandrogens cause a decrease in testosterone synthesis by the testes, resulting in similar rates of decreased libido and impotence as are observed with either DES or orchiectomy. These agents are also known to possess cardiovascular toxicity.[3,17]

Nonsteroidal antiandrogens work primarily by inhibiting uptake or nuclear binding of testosterone and DHT to androgen receptors. These receptors are found throughout the body in various tissues that depend on androgens. This includes activity at the hypothalamus, resulting in an increased secretion of LH and a consequent rise in the serum testosterone concentration through a negative-feedback inhibition. An increase in the serum testosterone concentration is of concern in patients with prostate cancer, since it may theoretically overcome the receptor-blocking activity of these compounds. However, clinical trials have not shown any decrease in response rate in association with this phenomenon.[18] On the contrary, the maintenance of a normal serum testosterone concentration in patients receiving monotherapy with an antiandrogen may have certain quality-of-life benefits, such as maintenance of libido. As noted earlier, an advantage of combining an LHRH analog with an antiandrogen at initiation of therapy is that the latter will prevent the temporary surge in LH and testosterone production associated with the LHRH analog.[19]

It is still unclear whether the nonsteroidal antiandrogens have other mechanisms that may be pertinent to their activity in prostate cancer. Some trials have demonstrated a moderate decrease in the concentrations of adrenal androgens in patients treated with nilutamide[20,21] while others have shown little[22] or no activity[23] of this agent on adrenal androgen production. Regardless of any effect on adrenal androgen production, the primary effect of nilutamide is thought to be due to the blockade of androgen receptors. In animal studies, the relative binding affinity of nilutamide for the androgen receptor is equivalent to that of hydroxyflutamide,[24] while the binding affinity of bicalutamide is approximately four times that of these other two agents.[25]

Pharmacokinetics

There are several differences in pharmacokinetics among the nonsteroidal antiandrogens.[26-29] The resulting differences in the recommended dosing of these agents are summarized in Table 1.[27-30] The majority of nilutamide's activity is attributable to the parent compound.[26,30] Only the nitro derivatives of nilutamide possess pharmacologic activity at the androgen receptor, and this is thought to be a minimal contribution to the overall effect. As noted previously, flutamide is a prodrug that must be converted to its active metabolite, hydroxyflutamide, after administration.[28] Currently, information is not available regarding the activity of the major urinary metabolites of bicalutamide, bicalutamide glucuronide, and hydroxybicalutamide glucuronide.[27]

Unlike hydroxyflutamide, with a half-life that appears to be approximately 6 hours, both bicalutamide and nilutamide have relatively long half-lives.[28,29,31] The available pharmacokinetic data indicate once-daily administration for both bicalutamide and nilutamide, while it is currently recommended flutamide should be taken three times daily. However, it is of interest that due to a lack of Phase I studies, the optimal therapeutic dosage of flutamide is unknown and the accepted dosage is based primarily on animal data.[18] All three agents are administered orally.

Nilutamide is eliminated as unchanged metabolites, with 49–78% of a radiolabeled dose recovered within 120 hours.[29] The microsomal cytochrome P450 system was responsible for much of the metabolism of nilutamide.[26] No dosing change appears to be warranted for nilutamide in patients with renal dysfunction, a known complication in patients with prostate cancer. Although hepatic impairment might be expected to prolong the elimination of nilutamide to some degree, via interference with its metabolism, no dosing changes are currently recommended. Bicalutamide is also extensively metabolized by the liver; however, a recent investigation failed to demonstrate any appreciable differences in pharmacokinetics between subjects with and without impaired hepatic function.[31] Hepatic dysfunction due to tumor involvement does not usually produce a severe dysfunction in the cytochrome P450 system; therefore, it is currently unknown whether any degree of hepatic dysfunction would warrant a decrease in dosage for these agents. Dosing changes are not currently recommended for either bicalutamide or flutamide in patients with renal or hepatic dysfunction.

Bioavailability was not determined in pharmacokinetic investigations of any of these agents due to the lack of a parenteral dosage form, although the negligible amount of radioactivity in the feces of these patients and the high urinary recovery led researchers to conclude that all agents were well absorbed.[27-29]

Table 1. Pharmacokinetics and Recommended Dosing of the Nonsteroidal Antiandrogens[27-30]

AGENT	$t_{1/2}$	DOSAGE	ELIMINATION ROUTE
Bicalutamide	5.8 d	50 mg/d	renal (inactive metabolites)
Flutamide	6 h	250 mg tid	renal (active metabolites)
Nilutamide	56 h	300 mg/d	hepatic (mainly inactive metabolites)

$t_{1/2}$ = half-life.

Clinical Studies

NONSTEROIDAL ANTIANDROGEN PLUS ORCHIECTOMY VERSUS ORCHIECTOMY ALONE

Four randomized, double-blind trials have been reported in the English literature comparing orchiectomy plus nilutamide with orchiectomy plus placebo (Table 2).[32-35] In all studies, the patients had histologically proven metastatic prostate cancer. A nilutamide dosage of 300 mg/d was used in all trials except the study by Brisset et al.,[32] which used dosages of both 150 and 300 mg/d. Data collected in all studies included the degree of bone pain, performance status using the Eastern Cooperative Oncology Group scale,[32-34] or the Karnofsky index,[35] symptoms of urinary obstruction, and both prostatic acid phosphatase (PAP) and alkaline phosphatase concentrations. Bone pain was assessed by patient interview and/or questionnaires[32-34] or by analgesic consumption.[35] Objective response was assessed using the response criteria of the National Prostatic Cancer Project, which included regression (complete or partial), stability and progression of disease, time to progression, and survival time.[36,37]

The result of changes in bone pain, performance status, and PAP concentrations are presented in Table 2. In three of the four studies, the nilutamide plus orchiectomy group had significant improvement in bone pain versus the placebo group at the completion of 6 months of therapy.[32,34,35] However, the only study evaluating differences in analgesic consumption between groups noted no difference in this variable.[35] Significant improvements in performance status after 6 months in favor of nilutamide plus orchiectomy were seen in only one study.[32] Therefore, it is doubtful that the decrease in pain observed in these trials was clinically significant, since the improvements in bone pain did not lead to improvements in performance status. It is possible that similar results may have been achieved by optimizing the analgesic therapy of these patients. Among patients who had elevated PAP concentrations at the beginning of therapy, there was no significant difference between those who received nilutamide and the control group in the normalization of this biochemical marker of bone metastasis after 6 months of therapy in any of the studies.[32-35]

The differences in patient response and survival are presented in Table 3. In evaluating best objective response to treatment at 6 months using the criteria of the National Prostatic Cancer Project, the percentage of patients who had regression of their disease was greater in the nilutamide-treated group in three of the four studies.[32-35] However, only one study demonstrated a significant difference in median time to progression.[35] In addition, this was the only study demonstrating even a trend toward significance in favor of nilutamide for actuarial survival rates.[35] In a previous trial of MAB, patients with minimal disease (defined as the absence of disease in the ribs, long bones, skull, or soft tissue other than lymph node involvement) demonstrated a greater response and survival rate than did patients with more severe disease.[36] These patients with minimal disease may indeed be the optimal candidates for MAB, since there may be a greater likelihood for delaying the emergence of resistant clones in this subpopulation. However, patients with minimal disease currently represent a minority of patients with metastatic prostate cancer, and these patients were not separately evaluated in the studies of nilutamide.

A meta-analysis of these nilutamide MAB trials calculated a 10% reduction in the annual odds of death in patients treated with nilutamide, but noted that this was not significant.[37] Currently, no studies have employed orchiectomy to compare nilutamide with either bicalutamide or flutamide. However, a meta-analysis evaluating MAB studies that used castration plus an antiandrogen has been recently published.[38] The antiandrogens used in these studies included nilutamide, flutamide, and cyproterone. The reduction in the annual odds-of-death rate was 6% for nilutamide and 9% for flutamide, neither of which were significant. These data further suggest that the two antiandrogens have a similar, albeit nonsignificant, impact on increasing the survival time of patients with advanced prostate cancer. It has also been demonstrated in at least one trial that the late addition (once patients had relapsed from the primary therapy) of a nonsteroidal antiandrogen to LHRH analog therapy in patients who had metastatic prostate cancer did not alter the rate of subsequent disease progression or survival.[39]

Table 2. Differences in Pain and Performance Status in Trials of Nilutamide With or Without Orchiectomy

	IMPROVEMENT IN BONE PAIN AT 6 MO (%)			CHANGES IN PAP AT 6 MO (% RETURN TO NORMAL)			IMPROVEMENT IN PERFORMANCE STATUS AT 6 MO		
REFERENCE	ORCH + PLACEBO	ORCH + NIL	p VALUE	ORCH + PLACEBO	ORCH + NIL	p VALUE	ORCH + PLACEBO	ORCH + NIL	p VALUE
Brisset et al. (1987)[32]	44 (n = 18)	94 (n = 17)	<0.01	59 (n = 26)	72 (n = 28)	NS	50 (n = 12)	90 (n = 36)	<0.01
Namer et al. (1990)[33]	81 (n = 27)	94 (n = 21)	NS	58 (n = 42)	69 (n = 33)	NS	57 (n = 40)	77 (n = 39)	NS
Beland et al. (1990)[34]	69 (n = 35)	86 (n = 50)	0.042	57 (n = 61)	68 (n = 61)	NS	NR	NR	NS
Janknegt et al. (1993)[35]	65 NR	78	0.03	57 NR	60	NS	71 NR	76	NS

NIL = nilutamide; NR = no data provided (no difference in performance status was noted at any time between the 2 groups); NS = not significantly different; ORCH = orchiectomy; PAP = prostatic acid phosphatase.

LHRH ANALOG PLUS A NONSTEROIDAL ANTIANDROGEN

The use of nilutamide in conjunction with an LHRH analog has been investigated in two randomized, placebo-controlled studies,[19,40] only one of which investigated the long-term effects of combination therapy.[40] Long-term effects were defined as those occurring 6–30 months after initiation of therapy. This latter study examined 26 patients receiving buserelin 500 µg/d sc plus nilutamide 300 mg/d po and 23 patients treated with buserelin 500 µg/d sc plus placebo. There were no significant differences between the groups in bone pain, impaired performance status, or elevated PAP at study entry. At the time of data analysis, patients had received 6–30 months of therapy. Efficacy analysis was performed on 22 patients in the control group and 16 patients in the nilutamide group. PAP returned to normal somewhat faster in the nilutamide group, although this difference was not significant. At 1 month of treatment there were significantly (no p value reported) more patients with improvement in bone pain in the nilutamide group (50% vs. 27%). There was also a reported improvement in performance status in patients receiving nilutamide at 1–6 months, although statistical data were not provided. No measurements of quality of life were performed; therefore, it is unclear whether these improvements in bone pain and performance status actually translated into a clinically significant improvement in quality of life for these patients. Disease progression rate decreased and time to progression increased in the patients who received nilutamide, although neither outcome variable was significantly different between the two treatment groups. There was also no significant difference in the number of deaths from cancer at 12 months between the two treatment groups.[40]

The other trial examined the impact of nilutamide in the control of LHRH-induced flare. In this randomized, double-blind, placebo-controlled trial by Kuhn et al.,[19] 36 men with metastatic prostate cancer received either buserelin 500 µg sc plus nilutamide 300 mg (n = 17) every morning or buserelin 500 µg sc plus placebo (n = 19). There were no significant differences in any study parameters between patient groups at entry. There was a significant difference in bone pain between the two groups at day 29, with fewer patients in the nilutamide group reporting an increase in bone pain. The median number of days for PAP concentrations to decrease by more than 75% from pretreatment values was also significantly less in the nilutamide group. Based on this small study, nilutamide appears to be a beneficial addition to therapy with an LHRH analog in short-term therapy.

Two studies[41,42] have evaluated the efficacy of flutamide combined with an LHRH analog compared with orchiectomy alone as the control in patients with metastatic prostate cancer. Both studies used goserelin plus flutamide as the MAB regimen. The European Organization for Research and Treatment of Cancer trial demonstrated a significant benefit for MAB in terms of time to first subjective progression (MAB 87 wk vs. orchiectomy 52 wk), time to progression (MAB 133 wk vs. orchiectomy 85 wk), and median duration of survival (MAB 34.4 mo vs. orchiectomy 27.1 mo) in a total of 310 patients.[41] However, a study of 262 patients by the Danish Prostatic Cancer Group failed to demonstrate any significant differences in these end points.[42] The reason for the different findings between these studies may be because the sample size in the Danish study was not calculated to detect a difference in overall survival of 20%. In addition, the risk of overlooking a survival benefit in this study was estimated to be 50%.

Several randomized, double-blind studies have evaluated the efficacy of flutamide versus placebo, each combined with an LHRH agonist. Crawford et al.[43] investigated the effectiveness of flutamide or placebo plus leuprolide in 603 patients with stage D_2 prostate cancer. Patients received flutamide 250 mg tid or placebo, plus leuprolide 1.0 mg/d sc. A significant (p = 0.039) difference in progression-free survival was observed in the treatment group. The estimated median progression-free survival time was 16.5 months for the flutamide group (95% CI 14.6 to 19.5) versus 13.9 months for patients receiving placebo (95% CI 11.8 to 15.3). Estimates of the length of survival was 35.6 months for the patients treated with flutamide and 28.3 months in the placebo group (95% CI 31.2 to 38.9 and 25.7 to 30.6, respectively). The difference in survival distributions was significantly in favor of the patients treated with flutamide. In this study, MAB was shown to be a superior therapy for the treatment of advanced prostate cancer over an LHRH agonist alone. However, a recent re-

Table 3. Response and Survival Results in Trials of Nilutamide With or Without Orchiectomy

	BEST OBJECTIVE RESPONSE AT 6 MO (%)			MEDIAN TIME TO PROGRESSION (mo)			MEDIAN SURVIVAL (mo)		
REFERENCE	ORCH + PLACEBO	ORCH + NIL	p VALUE	ORCH + PLACEBO	ORCH + NIL	p VALUE	ORCH + PLACEBO	ORCH + NIL	p VALUE
Brisset et al. (1987)[32]	33 (n = 39)	61 (n = 38)	0.05	13 (n = 43)	13 (n = 38)	NS	22 (n = 43)	24 (n = 38)	NS
Namer et al. (1990)[33]	52 (n = 59)	69 (n = 45)	0.09	NR	NR	NS	NR	NR	NS
Beland et al. (1990)[34]	20 (n = 89)	46 (n = 85)	0.001	12 (n = 96)	12 (n = 98)	NS	18.9 (n = 96)	24.3 (n = 98)	NS
Janknegt et al. (1993)[35]	24 (n = 184)	41 (n = 191)	≤0.001	14.9 (n = 145)	20.8 (n = 118)	0.005	30 (n = 216)	37 (n = 207)	0.071

NIL = nilutamide; NR = no data provided (it was reported that there were no significant differences between the 2 groups); NS = not significantly different; ORCH = orchiectomy.

view[44] noted at least five additional trials in a total of 1335 patients with metastatic prostate cancer in which no benefits in either survival or time to progression could be demonstrated with the combination of flutamide plus an LHRH agonist versus an LHRH agonist alone. It is unclear why the Crawford trial is the only major study to demonstrate an advantage of this MAB regimen with flutamide.

At least one trial has compared two different nonsteroidal antiandrogens in this type of MAB regimen for patients with metastatic prostate cancer. Schellhammer et al.[45] recently reported a randomized, double-blind study comparing bicalutamide with flutamide, each in combination with an LHRH agonist. A total of 813 patients were randomized in a 1:1 fashion to receive either bicalutamide 50 mg/d or flutamide 250 mg tid, plus a 2:1 randomization of goserelin acetate 3.6 mg q28d or leuprolide acetate 7.5 mg q28d. Analysis of the primary end point, time to treatment failure, after patients had completed a minimum of 6 months follow-up demonstrated a significant benefit for bicalutamide over flutamide (42% vs. 53%, respectively). The principal reason for the difference between the two treatment groups was a greater than tenfold excess in the number of patients discontinuing treatment secondary to diarrhea in the flutamide group.

There are currently no comparative studies evaluating nilutamide with either bicalutamide or flutamide, each in combination with an LHRH analog. While bicalutamide appears to have a more favorable efficacy/adverse effect profile than flutamide, it is unclear whether it will also prove to be superior to nilutamide in this type of MAB regimen.

ANTIANDROGEN WITHDRAWAL PHENOMENON

An interesting observation has been reported from clinical trials of MAB regarding the antiandrogen withdrawal phenomenon. It has been demonstrated that a subset (~40%) of patients who are being treated with either an LHRH analog or orchiectomy in combination with flutamide will benefit from withdrawal of the antiandrogen when relapse occurs.[46] This benefit has consisted of declines in serum prostate-specific antigen (PSA) in patients who had recently experienced an elevation in this disease marker. Some patients also experienced a reduction in clinical symptoms. However, the duration of decline in PSA was short-lived (median 5 mo).[46] A recent case series demonstrates that this phenomenon may occur with bicalutamide as well.[47]

It is currently unknown whether mutations of the androgen receptor or alterations of the androgen receptor binding site may have led to this paradoxic effect. It is also unknown whether this phenomenon will occur to the same degree with the three nonsteroidal antiandrogens. It is important that this temporary benefit from antiandrogen withdrawal not be ascribed to second-line hormonal therapy or chemotherapy that the patient may subsequently receive.

MONOTHERAPY

The use of a pure antiandrogen as monotherapy may offer an advantage in quality of life over MAB in the treatment of prostate cancer. Patients receiving nonsteroidal antiandrogen monotherapy do not experience significantly decreased libido or potency because serum testosterone concentrations are maintained.[48,49]

One study evaluated the merits of nilutamide monotherapy.[48] Twenty-six patients with untreated metastatic prostate cancer were enrolled in an open-label trial of nilutamide 100 mg q8h. Median progression-free survival was 9 months (range 6–35) and median survival was 23 months (range 12–48). A median of 6.5 months (range not reported) elapsed between progression and death. However, libido and potency were preserved in half of the sexually active men. In this small study, nilutamide monotherapy demonstrated moderate antitumor activity while still maintaining libido and potency in patients. However, the survival rate with monotherapy may be less than that achievable using MAB.[32-36,40,48]

Several Phase II studies of flutamide as monotherapy were reviewed.[17,18] The number of patients in each of the studies was small and, in the majority, patients with stage C or D disease were included. Some investigators treated patients who had received another form of hormonal therapy, making the results difficult to interpret.[18] The published response rates of patients receiving flutamide 750–1000 mg/d in these trials in comparison with historical controls receiving DES 1 mg/d did not demonstrate appreciable differences in response rates. In one randomized trial, flutamide 750 mg/d was compared with DES 3 mg/d.[50] Objective response or stabilization of disease was observed in 13 of 20 patients treated with flutamide compared with 8 of 20 patients treated with DES for 1 year. Based on the available data, flutamide monotherapy was not significantly superior to that achievable with standard hormone therapy.

Three trials have been conducted using bicalutamide 50 mg/d as monotherapy versus medical or surgical castration.[51-53] A Phase II monotherapy trial with bicalutamide was conducted to establish the initial response rate in patients with stage D_2 disease.[51] Long-term efficacy or survival was not evaluated in this study. Patients received bicalutamide 50 mg/d until progression of disease, death, or study withdrawal for any reason. Subjective response rates were based on the combination of changes in analgesic use, performance status, and patient scores for bone pain. Objective responses to treatment were defined as partial regression, progression, or stable disease. Best response was determined from month 6. Of 60 patients who were symptomatic at initiation of therapy, 30 (50%) responded (95% CI 36% to 64%). The objective response rate was 70%: 86 (57%) of the patients had partial regression, and 19 (13%) had stabilization of the disease. The authors concluded that bicalutamide was moderately effective as monotherapy in the treatment of patients with advanced prostate carcinoma but that it was not equivalent to medical or surgical castration.

In an open, randomized, multicenter trial, Chodak et al.[52] evaluated bicalutamide 50 mg/d versus surgical or medical (goserelin depot injection every 28 d) castration in patients with stage D_2 disease. Patients in both treatment groups also completed quality-of-life questionnaires. After a median of 39 weeks of therapy, there were significant

differences in treatment failure (53% with bicalutamide vs. 42% with castration) and disease progression (43% with bicalutamide vs. 33% with castration). Based on hazard ratios, either medical or surgical castration appeared to be superior to bicalutamide with regard to treatment failure and disease progression, although at the time of publication the median survival had not been reached for either treatment group. However, quality-of-life variables were significantly different between groups during the first 6 months of treatment and were in favor of bicalutamide. Hot flushes occurred less often with bicalutamide, although gynecomastia and breast tenderness were more common. The authors suggested that some patients might be willing to accept a treatment with some reduction in efficacy if the tradeoff in quality of life was sufficient.

The third trial[53] was a compilation of over 1000 patients from the previously cited trial by Chodak et al.[52] along with patients from two additional studies, again using bicalutamide 50 mg/d versus medical or surgical castration. All patients completed quality-of-life questionnaires during the first 6 months of therapy. Bicalutamide was again found to be significantly inferior to castration.[53] Treatment failure occurred in 53% (274/515) of patients in the bicalutamide treatment arm versus 41% (213/522) of patients in the castration group. Forty-six percent of patients in the bicalutamide treatment arm had objective progression of their disease (238/515) compared with 35% (182/522) of the patients in the castration group. However, survival was not significantly different between groups, with death occurring in 36% (213/595) of the patients treated with bicalutamide and in 35% (210/601) in the castration group. Median survival times were 25 and 28 months for bicalutamide and orchiectomy, respectively, after a median follow-up of 17 months. The quality-of-life assessments demonstrated advantages for bicalutamide with respect to sexual function and advantages for pain and bed disability with castration. Of particular interest were the differences in patient reports of overall health, social functioning, and emotional well-being. These parameters were favorable for bicalutamide during the first 3 months and then became more favorable for castration in the next 3 months. The authors attempted to explain this change in patient ratings for these quality-of-life parameters over time between the two treatments by noting that gynecomastia and breast tenderness (secondary to bicalutamide) take several months to develop and may worsen with time, while hot flushes (secondary to castration) occur immediately and may diminish with time.

The above trials of bicalutamide monotherapy suggest that bicalutamide 50 mg/d may be too low a dosage for effective monotherapy of prostate cancer. Blackledge[54] recently reviewed trials using high-dose bicalutamide monotherapy. This review provides evidence that bicalutamide 100 and 150 mg/d appear to yield similar results in terms of decreases in PSA concentrations to those achieved with medical or surgical castration. These higher dosages were reported to be well tolerated. It appears that the optimal dose of bicalutamide for monotherapy is still being defined, although a dosage greater than 50 mg/d will likely be necessary to approach the efficacy achievable with castration.

The issue of how to balance quality of life versus increased survival time is currently evolving. At least two recent trials[52,53] have systematically assessed quality of life in patients enrolled in trials of nonsteroidal antiandrogen monotherapy. However, such studies have not been performed to compare MAB with monotherapy. These initial quality-of-life data raise some questions with regard to which treatment options patients should be offered. This will only become more complex as the efficacy and toxicity data with higher dosages of bicalutamide monotherapy mature. Since most patients with metastatic prostate cancer will die of this disease regardless of the type of therapy they receive, the quality of their remaining life may be most important to them. Due to the previous lack of substantial data, some authors have stated that monotherapy (e.g., nilutamide) cannot be recommended at the present time.[16,55] However, others have suggested that allowing informed patients to make this choice may be advisable, rather than restricting such therapy.[52] No trials have been performed to compare nilutamide with other nonsteroidal antiandrogens as monotherapy, nor to determine which dosage of nilutamide may be most advantageous for this type of therapy in terms of response and impact on patient quality of life.

Adverse Effects

The most common adverse drug reactions reported with nilutamide, mostly from MAB trials, are provided in Table 4. Gastrointestinal and ophthalmic adverse effects are reported most frequently. A few of these adverse reactions are unique to nilutamide. These include light–dark adaptation disorders, alcohol intolerance, and interstitial pneumonia.[32-35,40,48,56-60]

In one reported series, adverse light–dark adaptation occurred in 67% (12/18) of patients.[56] All patients received nilutamide 300 mg/d. After bright illumination, the recov-

Table 4. Most Frequently Reported Adverse Effects with Nilutamide (% of Pts)

REFERENCE	PTS (n)	GI	ALCOHOL INTOLERANCE	OPHTHALMIC	PULMONARY
Brisset et al. (1987)[32]	38	3	17	28	5
Namer et al. (1990)[33]	72	31	NR	18	10
Beland et al. (1990)[34]	98	13	17	40	2
Janknegt et al. (1993)[35]	225	10	5	27	3
Navratil (1987)[40]	22	18	4	14	14
Decensi et al. (1991)[48]	26	42	19	31	NR

GI = gastrointestinal; NR = not reported.

ery time in these patients to adapt to dark increased to an average of 9 minutes (range 0.3–25), while the upper limit of normal adaptation is 1–2 minutes. When patients were changed to flutamide therapy, the visual symptoms rapidly disappeared. This adverse effect may be especially bothersome for some patients, especially those who drive at night.

Reversible interstitial pneumonitis is reported to occur in 1% of treated patients, as per the manufacturer's information.[57] However, in at least one study, interstitial pneumonitis was reported in 3% (12/411) of patients treated with nilutamide.[36] All patients experiencing this complication were hospitalized. Cumulative dose at the onset of symptoms ranged from 3 to 38 g (mean 21.5). The onset of pulmonary symptoms ranged from 10 days to 4 months (mean 80 d). The interstitial pneumonia reversed in all cases, with a recovery time ranging from days to weeks.[56-60] A possible mechanism responsible for this toxicity has been suggested by an investigation of the pulmonary metabolism of nilutamide in rats that demonstrated the production of a nitro anion free radical and subsequent generation of reactive oxygen species through redox cycling.[61]

There are differences among the trials of the nonsteroidal antiandrogens with regard to the reported frequency of certain endocrine adverse reactions. These differences are primarily due to whether an MAB regimen was used. For instance, the incidence of breast tenderness and gynecomastia secondary to nonsteroidal antiandrogens decreases substantially when these agents are used in MAB regimens (Table 5). However, except for one nilutamide monotherapy trial, which was conducted in a small number of patients,[48] the incidence of hot flushes is higher in patients receiving these drugs in MAB regimens. One unique adverse effect that seems to occur at a greater rate with flutamide in both MAB trials and monotherapy is diarrhea. This adverse reaction has been noted to occur in up to 24% of patients.[17,18,45]

The incidence of adverse reactions with nilutamide monotherapy is currently unclear, since most published experience with this agent is in MAB trials. The primary adverse reactions reported in monotherapy trials with bicalutamide include breast tenderness and gynecomastia, while with flutamide monotherapy the most common adverse reactions were diarrhea and gynecomastia (Table 5)![17,18,49,51,55,62-64] The reason for the higher incidence of gynecomastia and breast pain with monotherapy is the peripheral conversion of the excess testosterone to estradiol.[55]

As noted previously, antiandrogen monotherapy usually allows maintenance of libido, since testosterone secretion is not inhibited and these agents may actually result in an increase in plasma testosterone.[18] In a study using nilutamide 100 mg tid as monotherapy, libido and potency as defined by patients were preserved in roughly 50% of the patients.[48] A Phase II trial of bicalutamide 50 mg/d noted that 75% of patients were able to maintain libido.[51] Similar results have been seen with flutamide in regard to retaining libido.[17,18]

The impact of adverse reactions on the therapeutic success of these agents is not without consequence, as demonstrated by the recent trial comparing two MAB regimens using different antiandrogens (i.e., flutamide, bicalutamide).[45] The primary reason for the superior results in the bicalutamide treatment arm was a greater than tenfold rate of therapy discontinuation in the flutamide treatment arm secondary to adverse effects.

It is still unknown what impact these agents may have in terms of drug interactions. Agents that are extensively metabolized by the cytochrome P450 system (e.g., nilutamide) may result in significant interactions with other agents metabolized by this enzyme system. However, such interactions have not been reported in the published clinical experience with this agent and will likely not be known until it is used in a larger number of patients.

Therapeutic and Economic Issues

From the available published studies, the therapeutic impact of nilutamide or one of the other nonsteroidal antiandrogens in conjunction with either an LHRH analog or with castration in patients with metastatic prostate cancer is small. However, the cost of MAB to the patient and the healthcare system is quite considerable.

US pricing information on nilutamide was not available at press time. Based on the current retail cost of bicalutamide or flutamide, it is assumed that patients receiving nilutamide will pay approximately $300/mo for this agent. The monthly cost for an LHRH analog would add approximately $470.

The LHRH analog would typically be administered in the physician's office and therefore be covered by the patient's medical plan for patients covered under Medicare. The cost of the antiandrogen, however, would be covered under the patient's pharmacy benefit, which is paid out of pocket by many elderly Americans insured under Medicare. To justify this expense, objective data are needed to document the benefit of nilutamide either alone or in combination with an LHRH agonist over other less expensive

Table 5. Percent of Endocrine Adverse Drug Reactions Secondary to Nonsteroidal Antiandrogens

	BREAST TENDERNESS		GYNECOMASTIA		HOT FLUSHES		LIBIDO MAINTAINED	
ANTIANDROGEN	MAB	MONOTX	MAB	MONOTX	MAB	MONOTX	MAB	MONOTX
Flutamide[36,43,49,62-64]	4	NR	6–13	34–100	50	NR	NR[a]	50–100
Bicalutamide[49,51-53]	4	39–76	6	16–60	51	5–10	NR	75
Nilutamide[32,40,48]	NR	NR	NR	50	14–50	53	NR	47

MAB = maximal androgen blockade; MONOTX = antiandrogen monotherapy; NR = not reported.
[a]These MAB trials do not report maintenance of libido, since impotence occurs in virtually all patients.

therapies. Such data are lacking, and studies are unlikely to demonstrate a significant impact on survival rates except in patients with minimal disease who are initiating therapy.[31] However, such patients do not currently represent the majority of cases of diagnosed prostate cancer.

If one focuses on quality-of-life end points, the arguments for using an MAB strategy are even less convincing. Since patients may value maintenance of sexual potency over a relatively small increase in the survival rate, the issue of whether patients should be steered toward MAB is still controversial. When considering MAB for prostate cancer, an antiandrogen appears to have value in the first month of treatment with an LHRH analog, since it can prevent the possibility of disease flare. Beyond the first month of therapy, the benefits of MAB are less clear.

Although not endorsed by some authors because efficacy has not been demonstrated in randomized trials, the option of monotherapy with a nonsteroidal antiandrogen may be an attractive alternative for some patients. Monotherapy often maintains sexual potency, and other adverse effects (e.g., hot flushes) associated with markedly reduced concentrations of testosterone, similar to those obtained with castration, are usually avoided; however, an increased incidence of gynecomastia will occur. If monotherapy is considered, given their lower likelihood for producing bothersome adverse effects, either bicalutamide or flutamide may be more appropriate than nilutamide. With regard to adverse effects, published experience, and ease of dosing, bicalutamide appears to be the superior agent in this class at this time.

To make a recommendation regarding the role of nilutamide in the therapeutic armamentarium against metastatic prostate cancer, quality-of-life studies are needed. Such studies should compare the drug in MAB regimens with the other nonsteroidal antiandrogens and both as monotherapy and in MAB regimens versus orchiectomy, DES, and/or other nonsteroidal antiandrogen monotherapy. Until such trials can clearly define the place of nilutamide in the therapy of prostate cancer, nilutamide should not be considered as the antiandrogen of choice in the treatment of prostate cancer. For it to be chosen, nilutamide must be priced considerably less than either bicalutamide or flutamide and a patient must be able to tolerate its adverse effects.

Summary

Nilutamide will likely be the third nonsteroidal antiandrogen to be marketed in the US. Several randomized, placebo-controlled trials have documented its efficacy in combination with orchiectomy for the treatment of advanced prostate cancer. Measures of efficacy were limited mainly to improvements in response, and no trials demonstrated a significant improvement in patient survival. Although nilutamide also improved bone pain in most of these trials, concomitant improvements in performance status were often not observed and the impact on patient quality of life is questionable. Nilutamide also appears to have more serious adverse effects than the other currently marketed nonsteroidal antiandrogens. The cost of nilutamide will likely be comparable with that of bicalutamide and flutamide, which will be a substantial financial burden for many patients. The role of nilutamide either in MAB or as monotherapy is unclear at this time, and will likely remain so until it is compared with other agents and regimens in studies that also include analysis of patient quality of life. Nilutamide does not appear to offer advantages to patients beyond that achievable with currently available agents, and it should not be considered the antiandrogen of choice in the treatment of advanced prostate cancer. ≏

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EXTRACTO

OBJETIVO: Repasar la farmacología, farmacocinética, eficacia, y efectos adversos de nilutamida, y comparar este agente con los antiandrógenos

no esteroidales (bicalutamida y flutamida) mercadeados actualmente, a través de un análisis crítico de la literatura publicada.

FUENTES DE INFORMACIÓN: Se realizaron búsquedas en MEDLINE (1980–1995) y en Cancerlit (1991–1995) de publicaciones en el idioma inglés que utilizaran los términos "nilutamida," "bicalutamida," y "flutamida" solos y "nilutamida" o "antagonistas de andrógeno" en combinación con "neoplasmas prostáticos."

SELECCIÓN DE FUENTES DE INFORMACIÓN: Todos los artículos que trataron sobre nilutamida, bicalutamida, y flutamida fueron considerados para inclusión. Para estudios publicados en más de una revista, se usó la primera publicación, a menos que una publicación subsiguiente incluyera datos adicionales o más completos, citando en tal caso la última publicación.

MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Para formular conclusiones sobre eficacia clínica, se dió mayor prioridad a información obtenida de estudios empleando un diseño científico sólido (doble-ciego, al azar, controlado). Sólo información de estudios con grupos de tratamiento comparables con relación a tratamiento previo y severidad de la enfermedad fue incluída. Información sobre bicalutamida y flutamida también fue obtenida de estudios con diseño científico sólido para permitir comparaciones apropiadas con nilutamida.

SÍNTESIS: Nilutamida fue efectiva en combinación con orquiectomía en mejorar las respuestas de pacientes con cáncer de la próstata avanzado. Sin embargo, la supervivencia de pacientes no mejoró en estas pruebas, y mejoras en dolor de hueso usualmente no resultaron en un estado de funcionamiento mejorado en estos pacientes. Los pocos estudios de nilutamida como monoterapia o en combinación con un análogo de la hormona liberadora de hormona luteinizante son muy pequeños para hacer conclusiones significativas sobre su eficacia o su rol en el tratamiento de cáncer de próstata avanzado. Actualmente, no hay disponibles estudios comparativos de nilutamida con otros antiandrógenos, ni análisis sobre el impacto de nilutamida sobre la calidad de vida de pacientes. Nilutamida parece producir una frecuencia mayor de efectos adversos que los otros antiandrógenos no esteroidales, bicalutamida, y flutamida.

CONCLUSIONES: Nilutamida no parece presentar un avance mayor en el tratamiento de cáncer de próstata avanzado y parece ser un poco inferior a flutamida y bicalutamida con relación a efectos adversos. Nilutamida no se debe considerar como el antiandrógeno de selección en el tratamiento de cáncer de próstata avanzado.

BRENDA R MORAND

RÉSUMÉ

OBJECTIF: Réviser la pharmacologie, la pharmacocinétique, l'efficacité, et les effets secondaires du nilutamide et le comparer aux autres anti-androgènes (bicalutamide et flutamide).

REVUE DE LITTÉRATURE: Une recherche informatisée MEDLINE (1980–1995) et Cancerlit (1991–1995) utilisant les mots clés "nilutamide," "bicalutamide," et "flutamide" seul et "nilutamide" ou "antagoniste androgénique" en combinaison avec le terme "néoplasme prostatique" fut effectuée pour identifier la littérature de langue anglaise.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Tous articles portant sur le nilutamide, bicalutamide, ou le flutamide fut inclus. Pour les études publiées dans plusieurs journaux, seule la première publication fur référencée, à moins que les publications subséquentes n'ajoutent de l'information importante au sujet.

RÉSUMÉ: Le nilutamide est efficace en combinaison avec l'orchiectomie pour améliorer la réponse des patients avec un cancer prostatique avancé. Cependant, la survie des patients n'est pas prolongée dans ces études et les améliorations de la douleur osseuse ne résultent pas en une amélioration de la performance du patient. Les quelques études utilisant le nilutamide en monothérapie ou en combinaison avec un analogue LHRH sont trop petites pour en extraire des solides conclusions. Aucune étude comparative entre les anti-androgènes n'a été effectuée, de même aucune analyse du nilutamide sur la qualité de vie des patients n'est disponible. Ce médicament semble produire plus d'effets secondaires que les autres anti-androgènes.

CONCLUSIONS: Le nilutamide ne représente pas un avancement majeur dans le traitement du cancer prostatique avancé et semble être moins bien toléré que le bicalutamide et le flutamide. Il ne devrait pas être considéré comme l'anti-androgène de choix dans le traitement du cancer prostatique avancé.

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