Anti-Cancer Drugs 1999, **10**, pp. 791–796

Review paper

Which is the optimal antiandrogen for use in combined androgen blockade of advanced prostate cancer? The transition from a first- to second-generation antiandrogen

Michael F Sarosdy
Cancer Therapy and Treatment Center, San Antonio, TX 78229, USA.

Many physicians use combined androgen blockade in the form of a luteinizing hormone-releasing hormone analog or bilateral orchiectomy in combination with a non-steroidal antiandrogen to offer patients a potentially more effective treatment than castration alone. Three non-steroidal antiandrogens are available in the US, i.e. flutamide (Eulexin), bicalutamide (Casodex) and nilutamide (Nilandron). Nilutamide offers patients no benefit over flutamide or bicalutamide and has the least favorable safety profile. Because of its short half-life, flutamide must be administered 3 times a day. Furthermore, flutamide therapy is associated with a relatively high incidence of diarrhea, often intolerable for some patients. Bicalutamide is available in a convenient one tablet, once-a-day dosing regimen, is at least as effective as flutamide and is better tolerated in terms of diarrhea. Therefore, bicalutamide would seem to represent an appropriate first choice in patients who are suitable candidates for combined androgen blockade. [© 1999 Lippincott Williams & Wilkins.]

Key words: Antiandrogens, bicalutamide, flutamide, nilutamide, prostate cancer.

Introduction

Combining antiandrogen therapy with surgical or medical castration to block both adrenal and testicular androgen sources for the treatment of patients with advanced prostate cancer was proposed nearly two decades ago.[1] Although the view that combined androgen blockade (CAB) improves survival remains controversial, many physicians use CAB in the form of a luteinizing hormone-releasing hormone analog (LHRH-A) or bilateral orchiectomy in combination with a non-steroidal antiandrogen to offer patients a potentially more effective treatment than castration alone. Three non-steroidal antiandrogens are available in the US, i.e. flutamide (Eulexin), bicalutamide (Casodex) and nilutamide (Nilandron). Both flutamide and bicalutamide are approved by the Food and Drug Administration (FDA) for use in combination with LHRH-A therapy; nilutamide is approved for use in combination with bilateral orchiectomy. As with any drug, the choice of antiandrogen depends on multiple factors including efficacy, tolerability and convenience of administration. This article reviews the pharmacologic profiles and clinical trial data of each of the antiandrogens.

Pharmacokinetics of flutamide, bicalutamide and nilutamide

Flutamide, bicalutamide and nilutamide have different pharmacokinetic profiles and different dosing schedules. Flutamide is a prodrug that must be converted to hydroxyflutamide, the active metabolite, following oral administration.[2] There have been no systematic dose-finding studies of flutamide and therefore its optimal therapeutic dosage is unknown. Because the compound has a half-life of 5–6 h, flutamide requires oral administration every 8 h at a recommended dosage of 250 mg to maintain adequate plasma concentrations.[3] Given that once daily and twice daily regimens are associated with significantly better compliance than 3 or 4 times daily regimens,[4] the recommended administration schedule for flutamide is

This work was supported in part by contracts from AstraZeneca Pharmaceutical Co.

Correspondence to MF Sarosdy, South Texas Urology and Urologic Oncology, PA, 4499 Medical Drive, Suite 218, San Antonio, TX 78229, USA.
Tel: (+1) 210 615-3899; Fax: (+1) 210 615-3803;
E-mail: stxuro@txdirect.net

likely to be associated with non-compliance in some patients. Empiric or *ad hoc* underdosing is frequently mentioned by physicians, but no clinical data support this practice and reduced efficacy may result.

The pharmacokinetics of bicalutamide have been investigated in patients with prostate cancer who received single, oral doses of 10, 30 or 50 mg and higher. After repeated single, daily 50 mg doses of bicalutamide, the steady-state mean elimination half-life of the compound ranged from 7 to 10 days.[5] The long terminal half-life makes bicalutamide suitable for once daily dosing, a dosing schedule likely to maximize compliance in elderly patients.[6]

Nilutamide, like bicalutamide, has a relatively long half-life that supports once daily dosing. After multiple single doses of 100–300 mg, nilutamide mean elimination half-life ranged from 38 to 59 h.[7] The current recommended dose schedule of nilutamide is 300 mg once daily, taken as six 50 mg tablets, for the first 30 days of therapy, then 150 mg once daily.

Efficacy of flutamide, bicalutamide and nilutamide in combined androgen blockade

Flutamide plus medical or surgical castration versus castration alone

When viewed collectively, the results of randomized studies of CAB using flutamide and medical castration (LHRH) or surgical castration compared with castration alone (medical or surgical) are inconsistent (Table 1).[8–12] However, some of the studies lack sufficient power to detect a treatment effect of the expected magnitude. The results of the study (INT 0036) reported by Crawford *et al.*[8] suggested that there may be a particular benefit for patients with minimal disease and good performance status, but this observation was not confirmed in the Intergroup trial (INT 0105) of CAB versus orchiectomy reported by Eisenberger *et al.*[12] Although the results of the trials are different with respect to the benefit of flutamide in combination with castration, no study showed CAB with flutamide to be worse than either medical or surgical castration alone.

Bicalutamide plus LHRH-A versus flutamide plus LHRH-A

The Casodex Combination Study Group trial compared bicalutamide 50 mg once daily with flutamide 250 mg 3 times daily, each combined with LHRH-A therapy (leuprolide or goserelin) in patients with stage D2 prostate cancer.[13] This multicenter, randomized trial was double-blinded for antiandrogen therapy and open-label for LHRH-A therapy, with a 2×2 factorial design. Eight-hundred and thirteen patients were randomized 1:1 to bicalutamide or flutamide and 2:1 to goserelin (Zoladex) 3.6 mg or leuprolide (Lupron Depot) 7.5 mg every 28 days. With a median follow-up of 160 weeks, the median times to progression and death were 97 and 180 weeks for the bicalutamide plus LHRH-A group compared with 77 and 148 weeks for the flutamide plus LHRH-A group, respectively. The data indicate a trend favoring the bicalutamide plus LHRH-A group for both time to progression and survival, but the difference in treatment effect between the groups did not reach statistical significance.[13]

Table 1. Randomized trials of flutamide and medical or surgical castration versus castration alone

Investigators (*N*)	Treatment	Median progression-free survival (months)	*p* value	Median overall survival (months)	*p* value
Medical castration					
Crawford *et al.*	flutamide+leuprolide	16.5	0.039	35.6	0.035
(*N*=603)	placebo+leuprolide	13.9		28.3	
Surgical castration					
Iverson *et al.*	flutamide+goserelin	~17	0.69	~23	0.49
(*N*=264)	orchiectomy	~17		~28	
Denis *et al.*	flutamide+goserelin	~30	0.009	34	0.04
(*N*=327)	orchiectomy	~18		27	
Zalcberg *et al.*	flutamide+orchiectomy	–	–	23	0.21
(*N*=222)	placebo+orchiectomy	–		31	
Eisenberg *et al.*	flutamide+orchiectomy	20.4	0.26	35.5	0.14
(*N*=1387)	placebo+orchiectomy	18.6		29.9	

An exploratory analysis of the data from the Casodex Combination Study Group trial compared the efficacy and safety of the four CAB regimens used in the study.[14] Although such retrospective analyses must be interpreted with caution, analysis by the log-rank test, which accounts for proportional deaths over time, revealed that the leuprolide plus flutamide group had a significantly ($p < 0.005$) poorer outcome than any of the other three groups. These data suggest that leuprolide plus flutamide was the least effective among the four CAB regimens. Small differences between the LHRH-A therapies combined with differences between bicalutamide and flutamide may have contributed to the observed difference in survival.

Two additional exploratory analyses from this trial compared the effects of extent of disease and race on outcome for the bicalutamide plus LHRH-A and flutamide plus LHRH-A groups. Patients with minimal disease receiving bicalutamide plus LHRH-A demonstrated a trend to longer survival than those in the flutamide plus LHRH-A group, but the difference was not statistically significant. Among patients with extensive disease, treatment effects on disease progression and survival were similar among the four CAB regimens. Both white and black patients in the bicalutamide plus LHRH-A group had longer survival times than those in the flutamide plus LHRH-A group, although the difference between groups was not statistically significant (in preparation).

Nilutamide plus LHRH-A versus LHRH-A and nilutamide plus orchiectomy versus orchiectomy

Two trials assessed the long-term effects of nilutamide when combined with an LHRH-A. In one trial in 49 patients, no statistically significant difference in survival distributions was noted between a group of patients given nilutamide 300 mg per day together with the LHRH-A buserelin 500 μg/day and a group given buserelin alone.[15] A second trial involving 392 patients assessed the impact of adding nilutamide to leuprolide.[16] Although higher objective response rates were evident when nilutamide was added to leuprolide, no statistically significant differences between groups were seen for median times to progression and survival.

Four clinical trials[17–20] and one meta-analysis of the data from seven trials[21] evaluated nilutamide, predominantly in a daily dose of 300 mg, plus orchiectomy versus orchiectomy alone for patients with metastatic prostate cancer. None of the trials demonstrated a significant difference between the CAB group and the orchiectomy group in overall survival. One trial[20] did show a significant difference in favor of the nilutamide plus orchiectomy group for time to progression and a trend toward significance in overall survival. The meta-analysis[21] showed a benefit of nilutamide plus orchiectomy over orchiectomy alone in significantly reducing the odds of disease progression and reducing the odds of death from cancer.

Safety profiles of flutamide, bicalutamide and nilutamide

Flutamide

Based on the data from two large placebo-controlled randomized trials,[8,12] diarrhea was the most common adverse event associated with the use of flutamide (Table 2). Quality of life (QOL) outcomes were measured in study INT 0105.[12] Although most patients in this trial reported improved QOL over time, the patients receiving flutamide tended to show less improvement for most QOL measures.

Hepatic toxicity, including elevated transaminase levels, cholestatic jaundice and hepatic encephalopathy, has been reported in patients treated with

Table 2. Most common adverse events reported in placebo-controlled, randomized studies of combined androgen blockade with flutamide

Side effect	Most common adverse events (INT 0036)		Most common grade ≥2 events (INT 0105)	
	Leuprolide+placebo (%) (*N*=268)	Leuprolide+flutamide (%) (*N*=264)	Orchiectomy+placebo (%) (*N*=669)	Orchiectomy+flutamide (%) (*N*=667)
Diarrhea	4.9	13.6[a]	2.7	6.3[a]
Nausea/vomiting	14.2	11.8	4.4	4.1
Peripheral edema	4.9	4.9	–	–
Gynecomastia	12.7	13.3	–	–
Hot flashes	60.8	63.6	9.7	10.3

[a]Difference is statistically significant ($p \leq 0.002$).

flutamide therapy.[22] While the majority of cases of hepatic toxicity resolved with discontinuation of flutamide, there were isolated cases of liver failure and death.[23] Therefore, liver function tests are recommended for patients receiving flutamide and therapy should be stopped if transaminase levels exceed 2-3 times the upper limit of the normal range or if patients develop jaundice or other liver function abnormalities in the absence of hepatic metastases.

Bicalutamide

The safety profile of bicalutamide has been extensively reviewed.[24-27] Monotherapy trials established that breast pain and gynecomastia were the most common adverse events associated with bicalutamide treatment.[24] In the Casodex Combination Study Group trial, diarrhea occurred in significantly ($p<0.001$) fewer patients treated with bicalutamide compared with flutamide (Table 3).[13] Overall, diarrhea led to the withdrawal of two patients (0.5%) in the bicalutamide group and 25 (6%) in the flutamide group. Hematuria, in contrast, was reported in significantly ($p<0.007$) more patients in the bicalutamide plus LHRH-A group than in the flutamide plus LHRH-A group (12 versus 6%). Hematuria was unrelated to therapy for 98 and 92% of patients in the respective groups, and no patient withdrew because of this side effect.[13]

The markedly higher incidence of diarrhea associated with the use of flutamide reported in the Casodex Combination Study Group trial compared with that noted by Crawford *et al.* (26 versus 14%, respectively)[8] is explained by the fact that Crawford *et al.* reported only those instances of diarrhea attributed specifically to treatment with study drug. In contrast, the frequency of diarrhea reported in the Casodex Combination Study Group trial reflected the total incidence of the adverse event whether or not it was judged by the investigator to be related to the study drug.[13]

To date, there have been no published reports of fatal hepatotoxicity associated with the use of bicalutamide therapy. Abnormal liver function results were reported with a similar frequency for bicalutamide and for flutamide when each was combined with an LHRH-A.[28] Jaundice of unknown origin has been reported in five patients given bicalutamide.[25] One patient treated with bicalutamide for 2 days after receiving several weeks of flutamide therapy did develop fulminant hepatic failure,[29] but no causal relation to bicalutamide therapy has been established.[30,31]

Table 3. Most common (≥20%) adverse events, irrespective of causality (Casodex Combination Study Group trial)

Side effect	LHRH-A+ bicalutamide (%) (*N*=401)	LHRH-A+ flutamide (%) (*N*=407)
Hot flashes	53	53
Pain	35	31
Back pain	25	26
Constipation	22	17
Asthenia	22	21
Pelvic pain	21	17
Diarrhea	12[a]	26

[a]Difference is statistically significant ($p\leq0.001$).

Nilutamide

Hot flashes was the most common adverse event reported with the use of nilutamide in monotherapy or CAB trials,[32] occurring in approximately one-quarter to three-quarters of patients; gastrointestinal adverse events were reported in 3-42%.[33] A 'light-dark adaptation' disorder has been seen in from 13-57% of patients treated with nilutamide.[7] Patients may report a delay, ranging from a few seconds to a few minutes, in adapting to darkness after exposure to bright light and in some patients this effect does not abate unless therapy is discontinued. Many patients can tolerate this adverse event. However, all patients receiving nilutamide must be cautioned about night driving.

Pulmonary toxicity, specifically interstitial pneumonitis, represents a potentially serious side effect of nilutamide. This adverse event was first described in a series of eight case reports[34] and has since been reported in 2% of nilutamide-treated patients in controlled clinical trials.[7] In one controlled CAB trial, interstitial pneumonitis requiring withdrawal from therapy was reported in five of 112 patients (4.5%) receiving nilutamide plus orchiectomy, compared with no patients who received bicalutamide as monotherapy.[35] Patients with interstitial pneumonitis typically present with dyspnea, cough, chest pain and fever. Interstitial pneumonitis in nilutamide-treated patients normally resolves within days or weeks after withdrawal from therapy.[32]

Alcohol intolerance is another adverse event that appears to be specific to nilutamide reported in 5% of nilutamide-treated patients. This adverse event is typically characterized by skin rash, flushing, malaise or hyopotension.[7] It is uncommon for patients to discontinue therapy for this adverse event, but it may

affect compliance on days that patients drink alcohol.[6]

Conclusions

Physicians in the US prescribing CAB for patients with advanced prostate cancer can choose among three oral non-steroidal antiandrogens. Nilutamide offers patients no benefit over flutamide or bicalutamide and has the least favorable safety profile. Flutamide, the first antiandrogen to be commercially available, is generally well tolerated; however, it has features that limit its use. First, a short half-life requires 3 times daily administration. Second, flutamide therapy is associated with a relatively high incidence of diarrhea, often intolerable for some patients. Bicalutamide is available in a convenient one tablet, once-a-day dosing regimen, is at least as effective as flutamide and is better tolerated in terms of diarrhea. Therefore, bicalutamide would seem to represent an appropriate first choice in patients who are suitable candidates for CAB. Bicalutamide is also a logical alternative for patients who develop intolerable diarrhea while taking flutamide.

The relative merits of CAB compared to castration alone remain controversial. Many of the issues concerning the use of antiandrogens and CAB will not be resolved. None of these treatments is curative, and trials to investigate these issues would be very large, very expensive and very time consuming. In the absence of further clinical trial evidence, currently available information suggests the use of CAB when medical castration is employed and the selection of bicalutamide as the initial antiandrogen of choice.

References

1. Bracci U. Antiandrogens in the treatment of prostatic cancer. *Eur Urol* 1979; **5**: 303-6.
2. Katchen B, Buxbaum S. Disposition of a new, nonsteroid, antiandrogen, alpha,alpha,alpha-trifluoro-2-methyl-4'-nitro-*m*-propionotoluidide (Flutamide), in men following a single oral 200 mg dose. *J Clin Endocrinol Metab* 1975; **41**: 373-9.
3. Brogden RN, Clissold S. Flutamide. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in advanced prostatic cancer. *Drugs* 1989; **38**: 185-203.
4. Greenbergj R. Overview of patient compliance with medication: dosing: a literature review. *Clin Ther* 1984; **6**: 592-9.
5. Cockshott I, Cooper K, Sweetmore D, Blacklock N, Denis L. The pharmacokinetics of Casodex in prostate cancer patients after single and during multiple dosing. *Eur Urol* 1990; **18** (suppl 3): 10-7.
6. Kaisary A. Compliance with hormonal treatment for prostate cancer. *Br J Hosp Med* 1996; **55**: 359-66.
7. Harris M, Coleman S, Faulds D, Chrisp P. Nilutamide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in prostate cancer. *Drugs Aging* 1993; **3**: 9-25.
8. Crawford ED, Eisenberger M, McLeod D, *et al.* A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989; **321**: 419-24.
9. Iversen P, Christensen M, Friis E, *et al.* A phase III trial of zoladex and flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate. *Cancer* 1990; **66** (5 suppl): 1058-66.
10. Denis L, Carneiro De Moura J, Bono A, *et al.* Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. *Urology* 1993; **42**: 119-29.
11. Zalcberg JR, Raghaven D, Marshall V, Thompson P. Bilateral orchidectomy and flutamide versus orchidectomy alone in newly diagnosed patients with metastatic carcinoma of the prostate—an Australian multicentre trial. *Br J Urol* 1996; **77**: 865-9.
12. Eisenberger MA, Blumenstein B, Crawford E, *et al.* Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 1998; **339**: 1036-42.
13. Schellhammer PF, Sharifi R, Block N, *et al.* Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multicenter trial. Casodex Combination Study Group. *Urology* 1997; **50**: 330-6.
14. Sarosdy M, Schellhammer P, Sharifi R, *et al.* Comparison of goserelin and leuprolide in combined androgen blockade therapy. *Urology* 1998; **52**: 82-8.
15. Navratil H. Double-blind study of Anandron versus placebo in stage D2 prostate cancer patients receiving buserelin. Results on 49 cases from a multicentre study. *Prog Clin Biol Res* 1987; **243A**: 401-10.
16. Soloway M, Crawford E, Smith J, *et al.* A randomized, controlled trial of leuprolide and Anandron LA versus leuprolide and placebo for advanced prostate cancer. *Eur Urol* 1990; **18** (suppl): 99 (abstr 190).
17. Brisset J, Boccon-Gibod L, Botto H, *et al.* Anandron (RU 23908) associated to surgical castration in previously untreated stage D prostate cancer: a multicenter comparative study of two doses of the drug and of a placebo. *Prog Clin Biol Res* 1987; **243A**: 411-22.
18. Beland G, Elhiali M, Fradet Y, *et al.* A controlled trial of castration with and without nilutamide in metastatic prostatic carcinoma. *Cancer* 1990; **66** (5 suppl): 1074-9.
19. Namer M, Toubol J, Caty A, *et al.* A randomized, double-blind study evaluating Anandron associated with orchiectomy in stage D prostate cancer. *J Steroid Biochem Mol Biol* 1990; **37**: 909-15.
20. Janknegt R, Abbou C, Bartoletti R, *et al.* Orchiectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. *J Urol* 1993; **149**: 77-82.
21. Bertagna C, de Géry A, Hucher M, *et al.* Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostatic cancer. A meta-analysis of seven randomized double-blind trials (1056 patients). *Br J Urol* 1994; **73**: 396-402.

22. Wysowski DK, JP F, Tourtelot J, Horton MD. Fatal and nonfatal hepatotoxicity associated with flutamide. *Ann Intern Med* 1993; **118**: 860–4.
23. Wysowski D, Fourcroy J. Flutamide hepatotoxicity. *J Urol* 1996; **155**: 209–12.
24. Tyrrell C. Tolerability and quality of life aspects with the anti-androgen Casodex (ICI 176,334) as monotherapy for prostate cancer. International Casodex Investigators. *Eur Urol* 1994; **26** (suppl 1): 15–9.
25. Kolvenbag G, Blackledge G. Worldwide activity and safety of bicalutamide: a summary review. *Urology* 1996; **47**: 70–9.
26. Schellhammer P. Bicalutamide (Casodex). *Exp Opin Invest Drugs* 1996; **5**: 1707–22.
27. Goa KL, Spencer C. Bicalutamide in advanced prostate cancer. A review. *Drugs Aging* 1998; 1212: 401–22.
28. Schellhammer P, Sharifi R, Block N, *et al.* A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. Casodex Combination Study Group. *Urology* 1995; **45**: 745–52.
29. Dawson LA, Chow E, Morton G. Fulminant hepatic failure associated with bicalutamide. *Urology* 1997; **49**: 283–4.
30. Schellhammer P. Fulminant hepatic failure associated with bicalutamide. *Urology* 1997; **50**: 827.
31. Chodak G. Bicalutamide-associated fulminant hepatic failure. *Urology* 1997; **50**: 1027.
32. McLeod D. Tolerability of nonsteroidal antiandrogens in the treatment of advanced prostate cancer. *Oncologist* 1997; **2**: 18–27.
33. Dole E, Holdsworth M. Nilutamide: an antiandrogen for the treatment of prostate cancer. *Ann Pharmacother* 1997; **31**: 65–75.
34. Pfitzenmeyer P, Foucher P, Piard F, *et al.* Nilutamide pneumonitis: a report on eight patients. *Thorax* 1992; 622–7.
35. Chatelain C, Rousseau V, Cosaert J. French multicentre trial comparing Casodex (ICI 176,334) monotherapy with castration plus nilutamide in metastatic prostate cancer: a preliminary report. *Eur Urol* 1994; **26** (suppl 1): 10–4.

(Received 20 June 1999; accepted 29 June 1999)