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Review paper

Bicalutamide: a new antiandrogen for use in combination with castration for patients with advanced prostate cancer

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Maximum androgen blockade, a relatively recent development in the treatment of prostate cancer, combines medical or surgical castration with antiandrogen therapy. A large randomized study comparing the non-steroidal antiandrogen, bicalutamide, with flutamide, each in combination with luteinizing hormone-releasing hormone (LHRH) analogs, showed that after a median follow-up of 49 weeks, the time to treatment failure was significantly longer for the bicalutamide patients compared with the flutamide patients ($p = 0.005$). After a median follow up of 95 weeks, bicalutamide in combination with LHRH analog therapy produced at least equivalent efficacy with flutamide in combination with LHRH analog therapy in terms of time to treatment failure and equivalent efficacy in terms of survival. The tolerability profile of bicalutamide, as based on reported findings and a literature review, indicates a superior tolerability to that of currently available antiandrogens, particularly with respect to diarrhea with a low incidence of treatment-related withdrawals.

Keywords: Bicalutamide, combination therapy, prostate cancer.

Introduction

Prostate cancer is one of the most common malignancies of the male population world-wide and in many countries of the Western world it has become the most frequent, newly diagnosed cancer in men. In the US, it is the second most common cause of death from cancer, accounting for more than 13% of all cancer deaths and it was estimated that 200 000 new cases of prostate cancer were diagnosed in 1994.[1]

The growth of most prostate cancers is stimulated by the androgen testosterone, therefore a fundamental component of the therapy for this disease is androgen deprivation.[2] Following the work of Huggins,[3] bilateral orchidectomy has for many years been considered to be the 'gold standard' of hormonal therapy for advanced disease.[4] Since this pioneering work several methods of androgen deprivation have been developed; estrogens, luteinizing hormone-releasing hormone (LHRH) analogs and the antiandrogens, which block the effect of androgen on the receptor, have all been used in the treatment of prostate cancer.

Maximum androgen blockade (MAB), which combines castration (medical using an LHRH analog or surgical) with a steroidal or non-steroidal antiandrogen such as cyproterone acetate, nilutamide or flutamide, inhibits the effects of androgens from both the testes and adrenal glands. It could therefore improve the effectiveness of treatment for patients with advanced prostate cancer.[5] The concept of MAB as a therapy for prostate cancer was in fact originally conceived by Huggins and Scott in 1945,[6] whilst Bracci *et al.*[7] were the first to utilize combined androgen withdrawal by use of cyproterone acetate and bilateral orchidectomy.

Rationale for MAB

Surgical castration or LHRH analog therapy is effective in producing the withdrawal of androgens of testicular origin, and although this represents 95% of circulating testosterone, the production of adrenal androgens is not affected. These are converted to dihydrotestosterone (DHT), an important stimulus of androgenic action in the prostate cancer cell. As a result, after medical or surgical castration, the concentration of DHT in the prostate cell remains at approximately 40% of that measured in intact men,

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illustrating the need to also block the androgens produced by the adrenals.[8] In terms of efficacy it is accepted that LHRH analogs are equivalent to orchidectomy with regard to long-term pharmacodynamic action and clinical outcome (subjective and objective response, time to treatment failure, and survival).[9,10]

Although antiandrogen monotherapy may inhibit the action of androgens of testicular or adrenal origin, they compete with relatively high concentrations of testosterone for binding to the androgen receptor and have not, to date, been shown to be equivalent to castration. Castration removes the source of testicular androgens and therefore combining castration with an antiandrogen prevents even the remaining low levels of androgen from binding to the androgen receptor and stimulating tumour growth.

In 1982, Labrie *et al.*[11] reported the promising results of an open study of combination therapy with an antiandrogen and chemical castration. This approach offered an improved outcome compared with standard hormone manipulation.[3]

In 1989, the results of a large randomized double-blind study (National Cancer Institute) in 603 patients with metastatic prostate cancer showed that flutamide combined with an LHRH analog significantly improved time to progression and time to death, compared with treatment with an LHRH analog and placebo,[12] with a difference in median survival of 7.3 months ($p=0.035$). In a further study by the European Organization for the Research and Treatment of Cancer (EORTC) involving 310 patients, treatment with an LHRH analog combined with flutamide was associated with a statistically significantly longer time to progression and time to death than orchidectomy alone;[13] the benefit for the combination group in median survival was also 7.3 months ($p=0.02$). Recently, a meta-analysis of data from seven clinical trials comparing orchidectomy plus nilutamide with orchidectomy plus placebo in patients with previously untreated state D disease also showed the benefits of MAB on progression-free survival and overall survival.[14] However, a recent larger meta-analysis of all available randomized trials of MAB compared with castration alone, showed no significant difference in survival between the two treatment groups.[15] Nevertheless, while MAB remains the subject of some debate, all other studies which have compared medical or surgical castration plus placebo or antiandrogen have shown a significantly better or at least equivalent efficacy with the active combination therapy; none of these studies showed better efficacy for castration alone.[16–18] As a result, the use of MAB in the treatment of advanced prostate cancer is now becoming more widely accepted in clinical practice[13,14] and the results of the large ongoing South Western Oncology Group (SWOG) trial comparing orchidectomy plus flutamide versus orchidectomy plus placebo are eagerly awaited.

The non-steroidal antiandrogens (flutamide and nilutamide), which are currently available for the treatment of prostate cancer, can be associated with a number of undesirable side-effects,[19–23] with flutamide being associated with gastrointestinal disturbances (mainly diarrhea) and hepatic toxicity, whereas nilutamide can be associated with alcohol intolerance, visual disturbances and interstitial pneumonitis. Therefore a non-steroidal antiandrogen with at least comparable efficacy, but with fewer associated side-effects, would offer distinct benefits in the treatment of this disease.

This paper reviews the efficacy and tolerability of 'Casodex' (bicalutamide; 'Casodex' is a trademark, the property of ZENECA Ltd), a new non-steroidal antiandrogen for use in combination with castration in the treatment of patients with advanced prostate cancer. In particular it examines the efficacy of bicalutamide in combination with LHRH analog and the tolerability of bicalutamide during an extensive clinical trial program.

Bicalutamide clinical program

Patient population

Bicalutamide has been investigated as monotherapy and combination therapy over the last 7 years in more than 30 international clinical trials; exposing more than 3500 men to doses ranging from 10 to 200 mg daily. Almost 3000 of the men had advanced prostate cancer, with the large bicalutamide combination study[24] recruiting patients with stage D_2 prostate cancer and ranging disease extent (based on bone scan assessments). The patients were considered to represent the world-wide patient population requiring immediate hormonal therapy.

Dose selection for combination therapy study

Rationale. When the National Cancer Institute Study (036) was published in 1989,[12] which provided evidence of the effectiveness of combination therapy, bicalutamide was being investigated as a monother-

apy for advanced prostate cancer, at a range of doses (10–50 mg). It was therefore decided to the evaluate of bicalutamide as part of a combination therapy with castration. As flutamide (750 mg) was the most widely used antiandrogen in this setting, it was selected as the comparator.

The dose and dosing regimen of bicalutamide, for evaluation in the combination study, was chosen to have intrinsic activity in patients with advanced prostate cancer, efficacy at least equivalent to the comparator (flutamide), based on pre-clinical pharmacokinetic and pharmacodynamic data, supporting data to suggest that bicalutamide would have an additive effect to castration and an acceptable safety profile.

Selection of dose. A dose of 50 mg daily was chosen for the evaluation of bicalutamide as a component of combination therapy after comparing phase II bicalutamide results with published data for flutamide monotherapy (750 mg daily).[25] The decision was based on three reasons. Firstly, surrogate endpoint changes and efficacy after daily treatment with 50 mg bicalutamide in phase II and phase III monotherapy studies[26] were at least comparable with those reported with flutamide. Secondly, bicalutamide has a four times greater affinity for the androgen receptor than 2-hydroxyflutamide, the active metabolite of flutamide.[27] For, although steady-state plasma levels of bicalutamide are achieved more slowly than for 2-hydroxyflutamide, the relative binding potential to the androgen receptor, based on protein binding data (96% for bicalutamide versus 93% 2-hydroxyflutamide)[19,28] is greater for bicalutamide, even on the first day of therapy (Table 1). Thirdly, the known tolerability of bicalutamide suggested that 50 mg would be well tolerated in combination therapy.

Additive effect of bicalutamide and castration. Changes in serum prostate-specific antigen (PSA) concentrations have been shown to be sensitive indicators of response to hormonal therapy in prostate cancer and to be related to clinical outcome. In the 50 mg bicalutamide phase III monotherapy studies, a correlation was seen between the reduction in PSA concentration at month 3 compared with baseline and time to progression.[26] The observation that patients who had the largest decrease in PSA concentration also had a better treatment outcome has been confirmed by further statistical analyses. There was also clear evidence of a dose-related effect of bicalutamide on PSA after 3 months' treatment (Figure 1).

In published studies of nilutamide combined with castration, there were superior reductions in PSA concentration compared with castration alone, together with an increased number of patients in whom the PSA concentration normalized by 3 months.[29,30] Since changes to serum PSA are related to clinical outcome, the additive effects of antiandrogens plus castration on PSA suggest that the clinical outcome of combination therapy might be better than castration alone.

Results of the bicalutamide comparative trial

The comparative trial of bicalutamide and flutamide in combination with LHRH analog was a large randomized clinical study involving 813 patients (404 randomized to bicalutamide-LHRH analog and 409 randomized to flutamide-LHRH analog) from the USA and Canada. The main objective of this study was to compare the efficacy of bicalutamide (50 mg once daily) with flutamide (250 mg three times daily) each used in combination with the two most

Table 1. Antiandrogen levels and relative binding potential during the first week of treatment with bicalutamide (50 mg once daily) and flutamide (250 mg three times daily)

	Antiandrogen levels (ng/ml)				Binding potential ratio (bicalutamide/2-HF)
Day	total bicalutamide	total 2-HF[a,b]	free bicalutamide	free 2-HF	
1	901	940	36.0	66	2.18
2	1613	1500	64.5	105	2.46
3	2345	1500	93.8	105	3.57
4	2969	1500	118.8	105	4.53
7	4259	1500	170.36	105	6.49

[a] 2-HF = 2-hydroxyflutamide.
[b] 2-HF data was derived from refs 19 and 28.

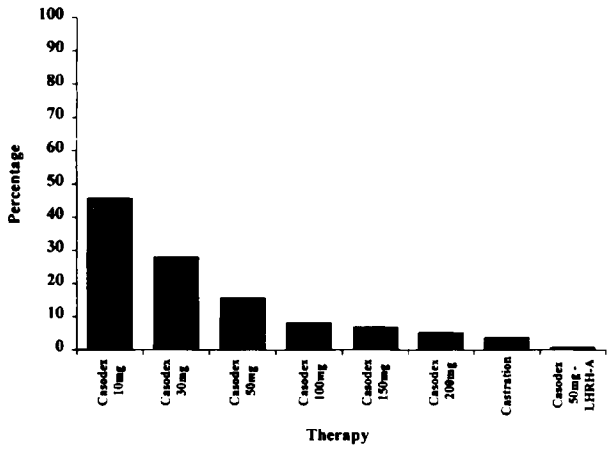

Figure 1. Median PSA remaining at 3 months.[26]

commonly used LHRH analogs, goserelin (3.6 mg injected s.c.) and leuprolide (7.5 mg injected i.m.) every 28 days. The study design was 2 × 2 factorial, with a double-blind comparison of bicalutamide and flutamide (randomized on a 1 : 1 basis) and a 2 : 1 randomization between goserelin or leuprolide, to create a background of medical castration against which the antiandrogens block the effect of remaining androgens. The study was designed to show equivalence with regard to time to treatment failure.

Time to treatment failure was chosen as the primary end-point since patients often withdraw from trials for reasons other than disease progression (e.g. due to toxicity) and such an end-point provides an unbiased assessment of treatment differences. In this study, treatment failure was defined as the first occurrence of either death, objective progression, addition of systemic or radiation therapy, or discontinuation of trial therapy for any other reason (e.g. adverse event, patient unwilling to continue, investigator decision).

The patients included in this study were typical of those patients with advanced prostate cancer, having different races, and extent of disease ranging from minimal evidence of metastases to extensive bone and soft tissue disease. These baseline characteristics were similar in the two treatment groups (Table 2).

The efficacy analysis included data from all patient visits completed by the date on which the last recruited patient had been followed for 6 months. After a median follow-up of 49 weeks, only 42% of patients randomized to bicalutamide-LHRH analog had reached a treatment failure end-point, compared with 53% of patients randomized to flutamide-LHRH analog. The hazard ratio of bicalutamide-LHRH analog therapy to flutamide-LHRH analog therapy was 0.749, indicating that patients treated with flutamide-LHRH analog were 34% more likely to fail treatment than those treated with bicalutamide-LHRH analog over the given time period. The two-sided 95% confidence interval (CI) was 0.61–0.92 and the upper one-sided 95% CI was 0.89. This result indicate that bicalutamide-LHRH analog was associated with a longer time to treatment failure than flutamide-LHRH analog ($p = 0.005$) when the data was analysed after a med-

Table 2. Demography of patients in the combination study[24]

	No. of patients (%)	
	bicalutamide-LHRH analog ($n = 404$)	flutamide-LHRH[a] analog ($n = 409$)
Age (years)		
mean	70	70
range	43–91	42–93
Race		
White	287 (71)	294 (72)
Black	95 (24)	91 (22)
Hispanic	13 (3)	19 (5)
other	9 (2)	5 (1)
Extent of disease on bone scan		
none	37 (9)	29 (7)
≤5 metastases	175 (43)	173 (42)
≥6 metastases	157 (39)	160 (39)
superscan[a]	24 (6)	27 (7)

[a] Superscan or its equivalent is defined as bone metastases in more than 75% of the ribs, vertebrae and pelvic bones.[10]

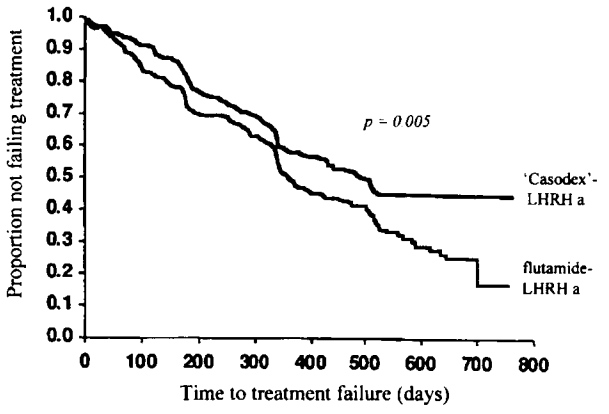

Figure 2. Kaplan Meier probability of treatment failure in the combination study.[24]

ian time to follow up of 49 weeks. However, a further analysis, with a median duration follow up of 95 weeks, produced results which are consistent with an improvement in time to treatment failure, although no longer significant compared to flutamide plus LHRH analogue. Based on an analysis when 34% of patients had died, bicalutamide plus LHRH analogue is equivalent to flutamide plus LHRH analogue in terms of survival.[24] (Figure 2).

When the data was analysed after a median follow up of 49 weeks, more patients in the flutamide-LHRH analog group withdrew from the study compared with bicalutamide-LHRH analog patients, accounted for mainly by the more than 10-fold greater number of patients on flutamide-LHRH analog who were withdrawn because of diarrhea (25 versus two patients). This represents a genuine difference, since antiandrogen therapy was double-blind. A number of other studies of flutamide in combination with an LHRH analog have also reported the withdrawal of flutamide patients due to adverse events (including diarrhea).[13,15,17,30]

During the first 200 days of treatment, the difference in treatment failure between the two groups was due to a greater number of patients in the flutamide-LHRH analog group withdrawing from treatment because of adverse events (39 versus 20 patients). Beyond this time, objective disease progression occurred more frequently in the flutamide-LHRH analog group (68 versus 45 patients; Table 3).

In this study, PSA had fallen by over 99% at 3 months; with 70% of patients recording PSA levels in the normal range at 3 months.

The method of castration used in the bicalutamide combination therapy study was LHRH analog (goserelin or leuprolide). The pharmacodynamic effect of LHRH analogs on the suppression of circulating androgens is equivalent to that achieved with surgical castration.[5,9] Furthermore, the benefit of combination therapy has been seen with both forms of castration[12,14] The addition of either one of these methods of castration to bicalutamide therapy can therefore be expected to have a similar clinical outcome, and since many physicians offer their patients a choice of castration method, either form of castration could be offered as part of a combination therapy regimen with bicalutamide.

In this trial, antiandrogen therapy was initiated at the same time as the LHRH analog. The study was not designed to evaluate a reduction of tumor flare and specific assessments to evaluate tumor flare occurrence were not included. Nevertheless, the number of patients reporting tumor flare as adverse events was very small; on case of tumor flare was reported as an adverse event in the bicalutamide-LHRH analog group and five in the flutamide-LHRH analog group.

Tolerability of bicalutamide

In comparative[32,33] and non-comparative[34,35] bicalutamide monotherapy studies, the most frequently reported adverse events were pharmacological;

Table 3. Reasons for treatment failure within three time intervals after initiating therapy in bicalutamide combination therapy study[24]

Reason for treatment	Time Interval (days)					
	0–200		201–350		351	
	bicalutamide-LHRH analog	flutamide-LHRH analog	bicalutamide-LHRH analog	flutamide-LHRH analog	bicalutamide-LHRH analog	flutamide-LHRH analog
Adverse event	20	39	4	7	8	10
Objective progression	28	30	35	39	10	29

gynecomastia and breast pain (approximately 26 and 34%, respectively), with a lower incidence of hot flushes (9%). When bicalutamide was given with LHRH analog therapy, the profile for these adverse events was reversed (5, 3 and 49%, respectively). Gynecomastia and breast pain are probably related to the unopposed action of circulating estrogen that occurs during bicalutamide monotherapy. In the presence of an LHRH analog, the circulating levels of both androgen and estrogen fall, thus explaining the lower incidence of gynecomastia and breast pain with bicalutamide-LHRH analog combination therapy and the increased incidence of hot flushes. The incidence of these events in the combination study was similar to that seen with flutamide-LHRH analog therapy (Table 4).

The withdrawal of androgenic stimulation of sebaceous gland activity may give rise to skin changes (dry skin, pruritis and rash) and therefore may also be considered to be pharmacological. The incidence of these events in the bicalutamide-LHRH analog study was low (less than 5%).

Non-pharmacological adverse events most frequently reported with bicalutamide-LHRH analog therapy (i.e. greater than 10%, regardless of causality) are presented in Table 5. These events include gastointestinal events and events related to the underlying disease. With the exception of diarrhea, the incidence of adverse events on bicalutamide-LHRH analog therapy was similar to that on flutamide-LHRH analog therapy. In combination therapy, the incidence of diarrhea is significantly less with bicalutamide than with flutamide (10 versus 24%, $p < 0.001$).

In the bicalutamide combination therapy study, fewer patients withdrew from therapy because of adverse events in the bicalutamide arm than in the flutamide arm (8 versus 14%, respectively). The difference was almost entirely due to the difference in withdrawals because of diarrhea (0.5 versus 6.1%).

In view of the known association between antiandrogens and hepatotoxicity,[20,36,37] particular attention was paid to the assessment of liver function in the bicalutamide clinical program. A review of the whole programme (bicalutamide-LHRH analog therapy and bicalutamide monotherapy) indicated that bicalutamide has infrequently been associated with elevations in transaminase levels and/or bilirubin concentrations. In many cases these changes were transient, resolving or improving despite continued bicalutamide therapy. There have been five cases of jaundice reported in which bicalutamide-induced hepatotoxicity cannot be excluded; however, there are no cases of liver failure attributed to bicalutamide therapy. In the combination study, liver function abnormalities were reported more frequently in the group of patients treated with flutamide-LHRH analog (10.3%) than in bicalutamide-LHRH analog patients (6.7%), although this difference was not statistically significant.

A literature review of nilutamide, as monotherapy and in combination with castration, demonstrates a 30–40% incidence of light/dark adaptation problems.[21,22] Alcohol intolerance, which occurs in around 20% of patients treated with nilutamide,[21,22] has only been reported in one patient receiving bicalutamide and was considered by the investigator to be unrelated to bicalutamide therapy. A small percentage of patients (1%) treated with nilutamide have developed interstitial pneumonitis,[23] this has not been reported with bicalutamide.

Conclusion

At a dose of 50 mg, in combination with castration, bicalutamide produces at least equivalent efficacy in patients with advanced prostate cancer compared with standard combination therapy, in terms of time to treatment failure and survival. It provides the convenience of once-daily oral administration, is well tolerated with a low incidence of treatment related withdrawals and a lower incidence of diarrhoea than flutamide. It can, therefore, be concluded that bicalutamide represents a new and useful alternative therapy to currently available antiandrogens when used in combination with castration in

Table 4. Incidence of pharmacological events during bicalutamide combination study[23]

	Bicalutamide-LHRH analog ($n=401$)	Flutamide-LHRH analog ($n=407$)
Gynecomastia	19 (4.7%)	24 (5.9%)
Breast pain	13 (3.2%)	11 (2.7%)
Hot flushes	196 (49%)	202 (50%)

Table 5. Non-pharmacological events most frequently reported (>10%) regardless of causality in bicalutamide combination study[23]

	Bicalutamide-LHRH analog ($n=401$)	Flutamide-LHRH analog ($n=407$)
Diarrhea	40 (10%)	98 (24%)
Nausea	44 (11%)	45 (11%)
Constipation	67 (17%)	50 (12%)
Asthenia	60 (15%)	69 (17%)
Back pain	62 (16%)	69 (17%)
Infection	41 (10%)	35 (8.6%)
Pain	109 (27%)	93 (23%)
Pelvic pain	52 (13%)	46 (11%)

the management of patients with advanced prostate cancer.

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