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Bicalutamide 150mg

A Review of its Use in the Treatment of Locally Advanced Prostate Cancer

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Data Selection

Sources: Medical literature published in any language since 1980 on 'bicalutamide', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'bicalutamide' and ('prostatic neoplasms' or 'prostate cancer'). EMBASE and AdisBase search terms were 'bicalutamide' and 'prostate cancer'. Searches were last updated 11 April 2006.

Selection: Studies in patients with locally advanced prostate cancer who received bicalutamide. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Bicalutamide, prostate cancer, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Bicalutamide (Casodex®) is a competitive androgen receptor antagonist that inactivates androgen-regulated prostate cell growth and function, leading to cell apoptosis and inhibition of prostate cancer growth. It is administered orally as a once-daily dose. In the EU and a number of other countries, bicalutamide 150 mg/day is approved in men with locally advanced nonmetastatic prostate cancer as immediate therapy either as an adjuvant to active treatment or as monotherapy as an alternative to surgical or medical castration.

Combined analysis of the three trials that comprise the bicalutamide Early Prostate Cancer (EPC) programme showed that bicalutamide administered in conjunction with standard care in men with locally advanced prostate cancer offers disease-free survival benefits over standard care alone and is generally well tolerated. Overall survival was improved to a greater extent in the subgroup of patients who received bicalutamide plus radiation therapy compared with radiation therapy alone. Men with localised prostate cancer do not benefit from the addition of bicalutamide to standard care. Combined analysis of two other studies in men with locally advanced prostate cancer show that bicalutamide monotherapy offers better tolerability and higher health-related quality-of-life (HR-QOL) scores for sexual interest and physical capacity compared with surgical or medical castration, while achieving disease-free and overall survival durations that were not significantly different. Thus, when treatment options are being evaluated, bicalutamide as adjuvant therapy or monotherapy should be considered as an alternative to other available hormonal therapies in men with locally advanced prostate cancer, especially in those who wish to maintain an active lifestyle.

Pharmacological Properties

Bicalutamide, a competitive androgen receptor antagonist, binds to cytosolic androgen receptors in prostate cells and inactivates androgen-regulated prostate cell growth and function. This leads to cell apoptosis and inhibition of prostate cancer growth. Unlike steroidal antiandrogens, bicalutamide has no progestogenic activity and does not suppress gonadotropin secretion or sex hormone production. Rather, it increases serum levels of luteinising hormone, testosterone, dihydrotestosterone, estradiol and follicle-stimulating hormone. Although increased estradiol levels may cause some unwanted hormonal effects, they protect against hot flushes and preserve bone mineral density.

After oral administration, the pharmacologically active (*R*)-enantiomer of bicalutamide is slowly and extensively absorbed. Mean steady-state plasma concentrations of (*R*)-bicalutamide are seen after about 4 weeks' administration of bicalutamide 150 mg/day in men with prostate cancer. (*R*)-bicalutamide is >99% bound to plasma albumin. Consistent with a long plasma half-life ($t_{1/2}\beta$) of almost 6 days, (*R*)-bicalutamide accumulates 10-fold after repeated administration. Bicalutamide undergoes extensive hepatic metabolism, and is excreted in approximately equal proportions in urine and faeces. In patients with severe hepatic impairment, the $t_{1/2}\beta$ of (*R*)-bicalutamide is increased 1.75-fold. Although metabolism of (*R*)-bicalutamide is predominantly mediated via the cytochrome P450 (CYP) 3A4 isoenzyme, there is no evidence of clinically significant drug interactions when bicalutamide ≤150 mg/day is coadministered with drugs that induce or inhibit CYP enzyme activity.

Therapeutic Efficacy

The efficacy of bicalutamide has been evaluated in conjunction with standard care in men with early (localised or locally advanced) prostate cancer in the EPC programme (n = 8113) and as monotherapy in men with locally advanced prostate cancer in two comparative studies. Combined data from the three EPC trials showed that bicalutamide plus standard care (watchful waiting, radical prostatectomy or radiation therapy) was more effective than standard care alone in improving objective progression-free survival in men with locally advanced prostate cancer at a median follow-up of 7.4 years. In addition, overall survival was improved to a greater extent in men with locally advanced prostate cancer who received bicalutamide plus radiation therapy compared with radiation therapy alone. Bicalutamide did not confer a progression-free or overall survival benefit to men with localised prostate cancer in the EPC programme.

Although equivalence could not be established, progression-free and overall survival durations with bicalutamide were not significantly different from those with surgical or medical castration at a median 6.3 years' follow-up in the combined results of the two monotherapy studies (n = 480). However, at 12 months' follow-up, HR-QOL scores for sexual interest and physical capacity were higher in bicalutamide recipients than in men who had been castrated.

Tolerability

The most frequently occurring adverse events associated with bicalutamide as adjuvant therapy or monotherapy were gynaecomastia and breast pain, although these adverse events were generally mild to moderate in severity. Adverse events, such as hot flushes (9.2% vs 5.4%), decreased libido (3.6% vs 1.2%), impotence (9.3% vs 6.5%) and abnormal liver function tests (3.1% vs 1.7%), and death from heart failure (1.2% vs 0.6%) were infrequent in both the bicalutamide and placebo arms in the EPC programme. In the monotherapy trials, the incidence of hot flushes in men who had been castrated was 50% compared with 13% in bicalutamide recipients. After 96 weeks' treatment in another trial, mean bone mineral density was maintained with bicalutamide, but had decreased in castrated patients.

1. Introduction

Prostate cancer is one of the most common forms of cancer affecting men, with an incidence second only to lung cancer in Europe[1] and the highest incidence of non-skin cancers in the US.[2] In Europe in 2004, an estimated 237 800 new cases of prostate cancer were diagnosed (16% of all new cancers in men) and an estimated 85 200 men died from the disease (9% of all cancer deaths in men).[1] In the US, 2006 estimates for new cases of prostate cancer and prostate cancer deaths are 234 460 (33% of new cases in men) and 27 350 (9% of cancer deaths in men).[2] Approximately two-thirds of men diagnosed with prostate cancer are aged >65 years,[2] with an average age at diagnosis of 71 years.[1] The incidence of new diagnoses of prostate cancer in Europe and the US has increased markedly since the early 1990s and cancers are being detected at an earlier stage, primarily due to the introduction of prostate-specific antigen (PSA) screening, improved diagnostic techniques and increased awareness of the disease.[3,4]

In general, three disease stages are recognised for prostate cancer.[3,5] Localised prostate cancer comprises Tumour Node Metastasis (TNM) stage T1 or T2 disease (confined to within the prostatic capsule with no lymph node involvement). Locally advanced prostate cancer comprises clinical stage T3 or T4 disease (disease extending beyond the prostatic capsule) with no lymph node involvement or distant metastases or residual disease after local treatment.[3,5] Advanced disease is evidenced by lymph node involvement or distant metastases.[3,5] Nevertheless, in practice, some patients with regional lymph node involvement and no distant metasta-

ses are considered to have locally advanced disease.[6,7] Patients with locally advanced disease comprise >30% of patients in unscreened populations presenting with prostate cancer.[7] Unlike those with localised tumours, men with locally advanced prostate cancer are at risk of disease progression and therefore require active treatment. However, there is no general consensus as to what is the most appropriate therapy.[5,8-10]

Treatment options include hormonal therapy, radiation therapy or a combination of the two modalities.[6] Surgery is not generally considered an option, because tumour removal is likely to be incomplete,[8] although some centres combine surgery with hormonal therapy and/or radiation therapy[3] or offer it as an option for selected patients.[5,10] Hormonal therapy predominantly involves androgen deprivation, either surgically (orchidectomy) or medically using luteinising hormone-releasing hormone (LHRH) analogues (such as leuprorelin or goserelin).[6] However, androgen blockade using the nonsteroidal antiandrogen bicalutamide (Casodex®)[1] is also an option.[5,6]

The role of bicalutamide in the management of early-stage (localised or locally advanced) prostate cancer has been briefly reviewed previously in *Drugs*;[11] the current article focuses on the role of bicalutamide in the management of locally advanced prostate cancer, now that longer-term efficacy and tolerability data are available.

2. Pharmacodynamic Properties

Bicalutamide is a competitive androgen receptor antagonist that prevents the physiological effects of dihydrotestosterone by binding to cytosolic androgen receptors in prostate cells.[12,13] It also blocks androgen-independent activation of the androgen receptor by cytokines (e.g. interleukin-6), growth factors (e.g. insulin-like growth factor-1) and signal transduction factors (e.g. protein kinase A), upregulates the androgen receptor co-suppressor nuclear receptor copressor and inhibits the co-activator steroid receptor coactivator-1.[12,14] Once bound to the androgen receptor, bicalutamide stimulates the assembly of a transcriptionally inactive receptor on DNA.[13] Inactivation of androgen-regulated prostate cell growth and function promotes apoptosis and leads to inhibition of prostate cancer growth.[12]

Bicalutamide is a racemate, with the (*R*)-enantiomer possessing most of the antiandrogenic activity.[15] *In vitro* studies have demonstrated that bicalutamide binds to androgen receptors in LNCaP human prostate tumour cells and inhibits androgen-stimulated gene expression and cell growth in various tumour cell lines.[16] It also dose-dependently inhibits cell proliferation in androgen receptor-positive human prostate cancer cell lines as well as in epithelial tumour cells obtained from men with prostate cancer.[17] In animal studies, oral bicalutamide has shown potent activity in reducing ventral prostate gland and seminal vesicle size in rats and monkeys, causing atrophy of the prostate gland and epididymides in dogs and suppressing the growth of Dunning R3227H prostate tumours in rats.[16]

Unlike steroidal antiandrogens, such as cyproterone, bicalutamide has no progestogenic activity and does not suppress gonadotropin secretion or subsequent sex hormone production.[18] Although earlier animal experiments showed a lack of hormonal effects with bicalutamide, suggesting a peripheral selective mechanism of action,[19] subsequent studies in men with advanced prostate cancer showed bicalutamide causes an increase in serum levels of gonadotropins and sex hormones.[18,19] This is presumably because bicalutamide exerts an antiandrogenic effect within the hypothalamic pituitary axis and blocks negative feedback inhibition by testicular androgens, thereby inducing an increase in serum levels of luteinising hormone and thus testosterone. Increases in dihydrotestosterone, estradiol and, to a lesser extent, follicle-stimulating hormone were also seen.[18,19]

Although increased levels of testosterone have the potential to reduce the clinical efficacy of antiandrogens, mean serum testosterone levels in men with prostate cancer during daily administration of bicalutamide 10–200mg remained within the reference range of normal, reached a plateau after 4–12 weeks of therapy, and were independent of dose.[20] The increase in estradiol levels, resulting from peripheral aromatisation of circulating androgens[18,21] as well as secretion of estrogen from the testes in the

1 The use of trade names is for product identification purposes only and does not imply endorsement.

presence of elevated gonadotropin levels,[18] is largely responsible for unwanted hormonal effects, such as gynaecomastia and breast pain. However, it is also protective against hot flushes (section 5) and may have a beneficial effect on bone mineral density (BMD), body composition and serum lipid levels compared with castration-based therapy.[22,23]

Indeed, two well designed studies have shown that bicalutamide 150 mg/day preserves BMD in patients with prostate cancer (table I). Men with localised,[22] recurrent[23] or locally advanced[22,23] prostate cancer were randomised to receive medical castration with a gonadotropin-releasing hormone (GnRH) analogue or bicalutamide 150 mg/day for 52[23] or 96[22] weeks. In patients who received bicalutamide monotherapy, BMD of the lumbar spine and total hip increased from baseline, but in those who underwent medical castration, BMD at these sites decreased; the differences between the two treatment groups were statistically significant (table I).[22,23] At the end of therapy, there were no significant differences between bicalutamide recipients and castrated patients in changes in fat-free mass (table I)[22,23] and bodyweight (+2.2% vs +3.2%).[23] Serum lipid levels (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol or triglycerides) in either treatment group did not change significantly from baseline after 96 weeks' treatment.[22]

3. Pharmacokinetic Properties

3.1 Absorption and Distribution

After oral administration, (*S*)-bicalutamide is rapidly absorbed and cleared from the plasma, whereas (*R*)-bicalutamide is slowly and extensively absorbed.[20] Plasma concentrations of (*R*)-bicalutamide after a single dose are 10- to 20-fold higher than those of the (*S*)-enantiomer. Consistent with its long elimination half-life ($t_{1/2}\beta$) [table II], (*R*)-bicalutamide accumulates 10-fold in plasma after repeated administration. Steady-state plasma concentrations of (*R*)-bicalutamide are 100-fold higher than those of the (*S*)-enantiomer. The mean peak plasma concentration (C_{max}) of (*R*)-bicalutamide after a single 150mg dose in healthy volunteers was 1.433 mg/L and was reached in 39 hours (table II).[20] The mean steady-state concentration of (*R*)-bicalutamide following repeated oral administration of bicalutamide 150mg in men with prostate cancer was 21.6 mg/L[20] and was achieved after about 4 weeks of daily administration. At steady state, (*R*)-bicalutamide accounts for 99% of the total circulating enantiomers.[20]

The pharmacokinetics of bicalutamide are unaffected by food.[20] Bicalutamide is extensively bound to plasma proteins (96.1% for the racemate; 99.6% for (*R*)-bicalutamide), predominantly to albumin.[20]

3.2 Metabolism and Elimination

Bicalutamide is extensively metabolised in the liver.[20] The major metabolic pathway for (*R*)-bicalutamide is hydroxylation followed by glucuronidation, whereas (*S*)-bicalutamide undergoes direct glucuronidation. Over a 9-day period, 36% of a single oral dose was excreted in the urine and 42% in the faeces. Glucuronide conjugates of bicalutamide and hydroxybicalutamide, but no parent compound, were found in the urine; bicalu-

Table I. Effects of bicalutamide (BIC) monotherapy or medical castration with a gonadotropin-releasing hormone analogue (GnRH) on bone mineral density (BMD) and fat-free mass (FFM) in men with localised,[22] recurrent[23] or locally advanced[22,23] prostate cancer. Results from two randomised, open-label, parallel-group studies

Study	Treatment (no. randomised)	Treatment duration	Results (% change from baseline)		
			Lumbar spine BMD	Total hip BMD	FFM
Sieber et al.[22]	BIC 150 mg/d (51)	96wk	+2.42**	+1.13**	−1.56
	GnRH[a] (52)		−5.40	−4.39	−3.86
Smith et al.[23]	BIC 150 mg/d (25)	52wk	+2.5**	+1.1*	−2.4
	GnRH[b] (26)		−2.5	−1.4	−3.6

a Specific GnRH not reported.

b Intramuscular depot administration of leuprorelin 22.5mg every 3mo.

* $p < 0.01$, ** $p < 0.001$ vs GnRH.

Table II. Mean pharmacokinetic parameters of bicalutamide in 28 fasting healthy volunteers after a single 150mg film-coated tablet[20]

Parameter	(*R*)-bicalutamide	(*S*)-bicalutamide
C_{max} (mg/L)	1.433	0.124
AUC_{∞} (mg • h/L)	325	3.95
t_{max} (h)	39	4
$t_{½\beta}$ (d)	5.57	1.45

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; **C_{max}** = peak plasma concentration; **$t_{½\beta}$** = plasma elimination half-life; **t_{max}** = time to C_{max}.

tamide and hydroxybicalutamide were found in the faeces, although these metabolites are thought to have been deposited in the bile as glucuronides and hydrolysed in the gut.[20]

(*R*)-Bicalutamide is eliminated much more slowly than the (*S*)-enantiomer (table II). Metabolism of (*R*)-bicalutamide appears to be mediated largely by cytochrome P450 (CYP) 3A4 isoenzymes, although drug interaction studies at bicalutamide dosages of ≤150 mg/day have shown no obvious potential for clinically significant drug interactions due to CYP enzyme induction or inhibition.[20]

Although increasing age, renal dysfunction or mild to moderate hepatic impairment do not affect the pharmacokinetics of bicalutamide, there is some evidence that the $t_{½\beta}$ of (*R*)-bicalutamide is significantly lengthened (by 1.75-fold) in patients with severe hepatic impairment.[20]

In *in vitro* studies, bicalutamide has been shown to displace warfarin from its protein binding sites; consequently, if bicalutamide therapy is started in patients already receiving warfarin or other coumarin anticoagulants, prothrombin time should be closely monitored.[24,25]

There was no evidence of pharmacokinetic interaction between bicalutamide and GnRH analogues when these agents were coadministered.[20]

4. Therapeutic Efficacy

The bicalutamide Early Prostate Cancer (EPC) programme comprises three randomised, double-blind, placebo-controlled trials evaluating the efficacy of bicalutamide in addition to standard care in men with early (localised or locally advanced) prostate cancer.[26] The three trials were conducted in North America (trial 23; n = 3292), Europe and 'the rest of the world' (trial 24; n = 3603) and Scandinavia (trial 25; n = 1218), and were designed and powered for combined analysis. A total of 8113 men (mean age 67 years) with localised, nonmetastatic prostate cancer (TNM stage T1–2, N0 or N not assessed, M0) or locally advanced, nonmetastatic prostate cancer (stage T3–4, any N, M0; or any T, N+, M0) were randomised to receive bicalutamide 150mg or placebo once daily. All patients received standard care (radiation therapy, radical prostatectomy or watchful waiting) in addition to randomised treatment. Two-thirds of patients entering the trials had localised disease and two-thirds had a Gleason score ≤6 at study entry.[26] The majority of patients were node negative or had not had node status assessed. None of those entering trial 23 and only 3.1% of those entering trials 24 and 25 had node-positive disease.[26]

Patients in trial 23 received randomised treatment for 2 years; patients in trials 24 and 25 received randomised treatment for ≥5 years or until disease progression. Inclusion criteria differed slightly in trial 23, in that candidates for watchful waiting and patients with lymph node involvement were excluded. The primary treatment strategy for patients in each trial differed: the majority of patients in trials 23 (80%) and 24 (65%) underwent primary curative therapy (radical prostatectomy or radiation therapy), whereas in trial 25, the majority of patients (81%) were managed conservatively (watchful waiting). Nevertheless, when data were combined, the two treatment groups were similar in terms of baseline disease stage, tumour grade, nodal status and initial therapy.[26]

The primary efficacy endpoints were objective progression-free survival (all trials) and overall survival (trials 23 and 25).[26] Progression-free survival was defined as time from randomisation to earliest occurrence of objective progression or death from any cause without progression.[26] Other endpoints included PSA progression-free survival, defined as time to PSA doubling from baseline, objective progression or death from any cause. The first, second and third per-protocol analyses of data from these trials occurred after a median follow-up of 3,[27] 5.4[28] and 7.4[29] years. Data presented are in the intent-to-treat population.[29]

The efficacy of bicalutamide has also been compared with that of surgical or medical castration in

480 men with locally advanced, nonmetastatic prostate cancer (PSA >20 ng/mL; stage T3–T4, M0) in two randomised, nonblind multicentre trials of identical design. Patients received bicalutamide 150 mg/day or castration; those undergoing castration could choose between bilateral orchidectomy or subcutaneous goserelin 3.6mg every 28 days. The primary endpoints were time to death, objective progression or treatment failure, and health-related quality of life (HR-QOL). Data from these trials were pooled as per protocol, and results from two analyses have been published: the first after a median follow-up of 4 years;[30] the second after 6.3 years' follow-up.[31] These studies were designed to demonstrate equivalence between bicalutamide and castration with regards to death, progression and treatment failure. To show equivalence, the upper 1-sided 95% confidence limit for the hazard ratio (HR) of bicalutamide to castration had to be less than 1.25.[31]

Most data are fully published,[26-33] with the remainder available as abstracts and/or posters.[34-36]

4.1 In Addition to Standard Care

4.1.1 Overall Population

Bicalutamide significantly ($p < 0.001$) improved objective progression-free survival in the overall population of the EPC programme (i.e. men with local or locally advanced disease) at a median follow-up of 7.4 years.[29] Disease progression was confirmed in 27.4% of bicalutamide and and 30.7% placebo recipients; the risk of disease progression was reduced by 21% with bicalutamide compared with placebo (HR 0.79; 95% CI 0.73, 0.85). After a median 7.4 years' follow-up, there was no significant difference in overall survival between groups; 22.8% of men in the bicalutamide group and 22.9% of those receiving placebo had died (HR 0.99; 95% CI 0.91, 1.09).[29]

In the individual trials, bicalutamide significantly improved progression-free survival compared with placebo in patients in trials 24 and 25, but there was no significant between-group difference in trial 23 (figure 1).[29] There were no significant between-group differences in overall survival in any of the individual trials.[29]

4.1.2 Subgroup Analyses

According to the study protocol, once a significant difference in progression-free survival between the treatment arms was detected in the combined analysis, prospectively defined subgroup analyses by stage and prior therapy were considered to determine where the benefit of bicalutamide therapy was greatest.[37]

Analysis of the combined data by stage at a median 3 years' follow-up showed that the risk of objective progression and PSA doubling was reduced with bicalutamide, irrespective of lymph node status.[32]

However, after a median 5.3 years' follow-up, results from trial 25 (primary therapy was predominantly watchful waiting) showed that compared with placebo, bicalutamide improved survival in men with locally advanced disease (HR 0.68; 95% CI 0.50, 0.92), but decreased survival in those with localised disease (HR 1.47; 95% CI 1.06, 2.03).[33] In light of these findings, exploratory analyses of data by disease stage across the three trials and by individual trial were carried out. Data from subsequent follow-up assessments in men with localised disease are discussed in this section, while those for men with locally advanced disease are discussed in section 4.1.3.

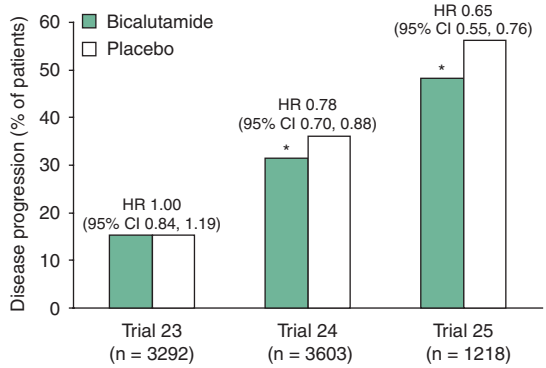

Fig. 1. Efficacy of bicalutamide as adjuvant therapy in early prostate cancer. Objective progression-free survival in the three randomised, double-blind, placebo-controlled trials of the Early Prostate Cancer programme after a median follow-up of 7.4 years. Men with localised or locally advanced prostate cancer received standard care (radical prostatectomy, radiation therapy or watchful waiting) in addition to either bicalutamide 150 mg/day or placebo.[29] **HR** = hazard ratio; * $p < 0.001$.

At 7.4 years, there were no significant differences in the combined analysis between bicalutamide and placebo in terms of progression-free survival or overall survival in men with localised prostate cancer, irrespective of underlying therapy.[29] However, the likelihood of decreased survival with bicalutamide in men for whom watchful waiting was the primary therapy approached statistical significance (HR 1.16; 95% CI 0.99, 1.37; p = 0.07).[29] In individual trial results, the likelihood of a survival disadvantage approached statistical significance in men with localised disease in trial 25 at a median follow-up of 7.1 years (HR 1.23; 95% CI 0.96, 1.58; p = 0.11).[35]

At a median 5.4 years' follow-up, exploratory analyses showed that bicalutamide significantly (p < 0.001) improved PSA progression-free survival in men with localised disease compared with placebo, irrespective of primary therapy (reported as an abstract and poster).[34] Results for PSA progression-free survival at 7.4 years have not been published.

4.1.3 Locally Advanced Prostate Cancer

Bicalutamide significantly increased progression-free survival in men with locally advanced prostate cancer at a median follow-up of 7.4 years, irrespective of underlying therapy.[29] Disease progression in bicalutamide versus placebo recipients was significantly (p < 0.001) reduced in those undergoing adjuvant therapy compared with standard care in the combined analysis.[29] The risk of disease progression with bicalutamide compared with placebo was reduced by 25%, 44% and 40% in men with locally advanced disease undergoing radical prostatectomy, radiation therapy or watchful waiting, respectively (figure 2).

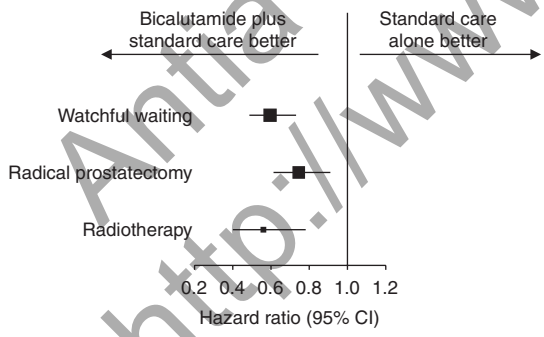

Fig. 2. Progression-free survival with bicalutamide as adjuvant therapy in men with locally advanced prostate cancer. Results from the Early Prostate Cancer programme after a median follow-up of 7.4 years are shown as hazard ratios. Patients with locally advanced prostate cancer received standard care (radical prostatectomy [n = 1719], radiation therapy [n = 305] or watchful waiting [n = 657]) in addition to either bicalutamide 150 mg/day or placebo.[29] The size of the hazard ratio square is in proportion to the number of events reported.

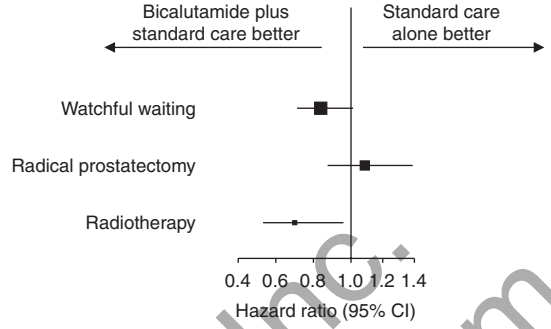

Fig. 3. Overall survival with bicalutamide as adjuvant therapy in men with locally advanced prostate cancer. Results from the Early Prostate Cancer programme after a median follow-up of 7.4 years are shown as hazard ratios. Patients with locally advanced prostate cancer received standard care (radical prostatectomy [n = 1719], radiation therapy [n = 305] or watchful waiting [n = 657]) in addition to either bicalutamide 150 mg/day or placebo.[29] The size of the hazard ratio square is in proportion to the number of events reported.

Overall survival was significantly improved in bicalutamide recipients with locally advanced prostate cancer undergoing adjuvant radiation therapy (35% reduction in risk; figure 3), but there was no statistically significant effect on survival in patients undergoing radical prostatectomy or watchful waiting. The improved survival in bicalutamide recipients receiving radiation therapy was driven by a reduced incidence of prostate cancer-related death with bicalutamide than with standard care (16.1% vs 24.3%).[29]

In men with locally advanced disease undergoing watchful waiting, the likelihood of increased survival with bicalutamide at 7.4 years approached statistical significance in the combined analysis (figure 3).[29] This was largely because of the result from trial 25,[29,33] in which a statistically significant survival advantage with bicalutamide was seen at a median follow-up of 7.1 years in men with locally advanced disease undergoing watchful waiting (HR 0.67; p = 0.007) [reported as an abstract and oral presentation].[35] In trial 24, bicalutamide recipients

with locally advanced prostate cancer who would have otherwise undergone watchful waiting showed no significant improvement in overall survival compared with watchful waiting alone.[29]

Exploratory analyses at a median 5.4 years' follow-up showed that in addition to standard care, bicalutamide significantly ($p < 0.0001$) improved PSA progression-free survival in men with locally advanced disease compared with placebo in the combined analysis (HR 0.42; 95% CI 0.38, 0.47; reported as an abstract and poster).[34] PSA progression-free survival was significantly reduced by 52%, 60% and 68% in bicalutamide recipients undergoing radical prostatectomy (HR 0.48; 95% CI 0.41, 0.56), radiation therapy (HR 0.40; 95% CI 0.29, 0.56) or watchful waiting (HR 0.32; 95% CI 0.26, 0.39) [all $p < 0.0001$ vs placebo].[34] Results at a median 7.4 years' follow-up are not yet available.

4.2 As Monotherapy Compared with Castration

Although overall survival duration and time to disease progression after a median 6.3 years' follow-up were not significantly different with bicalutamide or castration in men with locally advanced prostate cancer, equivalence between the treatments was not demonstrated.[31] At this timepoint, 77% of trial participants had evidence of disease progression, irrespective of treatment, and 56% had died. There was no significant difference between bicalutamide and castration for overall survival (HR 1.05; 2-sided 95% CI 0.81, 1.36; $p = 0.70$) or time to disease progression (HR 1.20; 2-sided 95% CI 0.96, 1.51; $p = 0.11$). Statistical equivalence between the two treatments could not be established, based on the upper 1-sided 95% confidence intervals (1.31 for overall survival duration and 1.45 for time to disease progression).[31]

Nevertheless, with respect to HR-QOL factors, bicalutamide recipients had significantly greater sexual interest ($p = 0.029$) and physical capacity ($p = 0.046$) at 12 months than men who had been castrated. No other significant differences were seen in any of the other HR-QOL parameters (emotional well being, vitality, social function, pain, activity limitation, bed disability, overall health).[30,31]

5. Tolerability

The most common adverse events associated with bicalutamide 150 mg/day in the EPC programme[29] and the monotherapy studies comparing bicalutamide 150 mg/day with castration[31] were breast pain and gynaecomastia. After a median follow-up of 7.4 years, the incidence of breast pain was 73.6% and that for gynaecomastia was 68.8% in men with localised or locally advanced prostate cancer who received bicalutamide 150 mg/day in addition to standard care (figure 4).[29] In >90% of affected patients, these events were mild to moderate; 16.8% and 0.7% of bicalutamide or placebo recipients withdrew from treatment because of breast pain and/or gynaecomastia. The incidences of hot flushes (9.2% vs 5.4%), decreased libido (3.6% vs 1.2%), impotence (9.3% vs 6.5%) and abnormal liver function tests (3.1% vs 1.7%) in bicalutamide versus placebo recipients were relatively low. Overall, 29.3% and 10.0% of bicalutamide or placebo

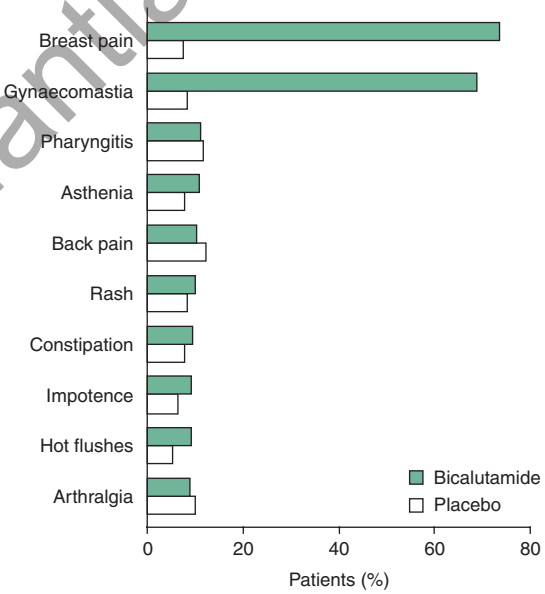

Fig. 4. Tolerability of bicalutamide. The most common adverse events (>9% in either treatment arm) reported in the combined results of the Early Prostate Cancer programme after a median follow-up of 7.4 years. In three randomised, double-blind studies, men with localised or locally advanced prostate cancer received standard care (radical prostatectomy, radiation therapy or watchful waiting) in addition to either bicalutamide 150 mg/day (n = 4022) or placebo (n = 4031).[29]

recipients discontinued treatment because of adverse events.[29]

The incidence of gynaecomastia and breast pain was 49.4% and 40.1% in men with locally advanced prostate cancer who received bicalutamide monotherapy, compared with 4.4% and 1.9% in castrated patients.[31] Hot flushes, however, occurred in 50.0% of castrated patients compared with 13.1% of bicalutamide recipients. Other adverse events in bicalutamide versus castration recipients included diarrhoea (6.4% vs 12.5%), abdominal pain (10.5% vs 5.6%) and asthenia (11.5% vs 7.0%). Among bicalutamide recipients, 4.1% discontinued treatment because of adverse events; 1.3% of patients withdrew because of breast pain and/or gynaecomastia.[31]

Mean BMD of the lumbar spine and total hip was preserved with bicalutamide 150 mg/day in a 96-week study in men with localised or locally advanced prostate cancer,[22] whereas significant reductions in mean BMD at these sites were seen in those undergoing medical castration (section 2).

The incidence of abnormal liver function tests reported as an adverse event in the first analysis of the EPC programme at median follow-up of 3 years was 3.4% and 1.9% in the bicalutamide and placebo groups.[27] Clinically relevant increases in AST, ALT and bilirubin were seen in 1.6%, 1.6% and 0.7% of bicalutamide recipients and 0.5%, 0.3% and 0.4% of placebo recipients. However, it was noted that these events were usually transient and rarely severe.[27] Nonetheless, periodic liver function tests are recommended during treatment with bicalutamide (section 6).[24,25]

At 7.4 years' follow-up, numerically fewer bicalutamide than placebo recipients had died because of prostate cancer (6.4% vs 7.5%), but numerically more bicalutamide than placebo recipients had died of non-prostate cancer causes (10.2% vs 9.2%).[29] There were numerically more deaths from heart failure (1.2% vs 0.6%) and gastrointestinal carcinoma (1.3% vs 0.9%) in bicalutamide versus placebo recipients, although no consistent pattern was seen to suggest a drug-related toxicity.[29]

6. Dosage and Administration

Bicalutamide 150mg is indicated in the EU and elsewhere as immediate therapy either alone or as adjuvant to treatment of curative intent (e.g. radical prostatectomy or radiation therapy) in men with locally advanced prostate cancer or as monotherapy in men with locally advanced nonmetastatic prostate cancer for whom immediate hormonal therapy is indicated (i.e. as an alternative to castration).[24,25] Local prescribing information should be consulted, as the indication differs in some countries.

The recommended dosage of bicalutamide for use in men with locally advanced prostate cancer, either alone or as adjuvant to treatment of curative intent is 150mg once daily for a minimum duration of 2 years.[24,25]

No dosage adjustments are required for the elderly or in patients with renal dysfunction, but caution is required in patients with moderate to severe hepatic impairment. Because of the possibility of hepatic changes during bicalutamide therapy (section 5), periodic liver function testing is recommended.[24,25]

Local prescribing information should be consulted for other contraindications, warnings and precautions.

7. Place of Bicalutamide in the Management of Locally Advanced Prostate Cancer

The purpose of active treatment in men with locally advanced prostate cancer is to prevent disease recurrence, thereby minimising the impact of the disease on patient HR-QOL, and improve overall survival.[6,38] Hormonal therapy (generally surgical or medical castration), with or without radiation therapy, is associated with significant improvements in progression-free and/or overall survival in men with locally advanced prostate cancer,[38] and is considered an appropriate first-line therapy for this disease stage in various treatment guidelines.[3,5,9,10] However, in the context of the trend for prostate cancer being diagnosed at an earlier stage and in younger men, tolerability and HR-QOL issues, particularly those relating to sexual and physical activity, are equally as important as survival benefits when making treatment decisions.[5,38-40]

Androgen deprivation achieved via surgical castration (orchidectomy) is the gold standard against which other androgen deprivation therapies are assessed, although it is associated with a negative psychological effect that may be unacceptable to patients, especially younger, sexually active men.[5] Medical castration, which is considered a more acceptable alternative, is achieved using long-acting LHRH analogues, of which goserelin[41-44] is the most extensively studied. Clinical trials have shown that surgical or medical castration as an alternative to watchful waiting or as an adjuvant to radical prostatectomy or radiation therapy generally confers significant clinical benefits in terms of delaying disease recurrence and improving overall survival.[5] However, this benefit may be at the expense of sexual interest and function. Castration therapy is also associated with an increased incidence of fatigue, muscle wasting and increase in body fat, hot flushes, osteoporosis and osteoporotic fractures, anaemia and possibly loss of cognitive function due to the absence of testicular androgens, including testosterone.[5,8,39,45] Nevertheless, many of these adverse events can be effectively managed.[5,8]

Bicalutamide is the most extensively studied nonsteroidal antiandrogen and is the only one recommended as an alternative primary therapy to medical or surgical castration in locally advanced prostate cancer.[5] The EPC programme, which comprised three clinical trials conducted in North America, Scandinavia and Europe and the 'rest of the world', was designed to assess the efficacy of adding bicalutamide to standard care in men with either localised or locally advanced nonmetastatic prostate cancer (section 4.1). All three trials had common efficacy endpoints, but treatment durations differed; the North American trial was limited to 2 years, while that in the other trials was ≥5 years or until disease progression. The prognosis and management of the patient populations differed across the individual trials, because of the different disease management practices across the countries in which the trials were conducted. Prognosis was best in the North American trial and worst in the Scandinavian trial; however, the baseline characteristics of the two treatment groups were similar when the data were combined (section 4.1).

Even though early in the EPC programme combined results indicated that progression-free survival was significantly improved with addition of bicalutamide to standard care compared with standard care alone, it became apparent on subgroup analysis that this benefit was limited to men with locally advanced prostate cancer (section 4.1). In men with localised disease, the balance of risk : benefit ratio with bicalutamide was unfavourable (section 4.1.2) and approval for its use in this patient population was withdrawn in the UK and Canada.[46,47]

While the addition of bicalutamide to standard care conferred no overall survival benefit compared with standard care alone after a median 7.4 years' follow-up in the combined analysis of the EPC programme, the beneficial effect of adjuvant bicalutamide on progression-free survival in the subgroup of men with locally advanced prostate cancer was evident, irrespective of the type of standard therapy (watchful waiting, radical prostatectomy or radiation therapy). Moreover, the addition of bicalutamide to radiation therapy improved overall survival compared with radiation therapy alone in these patients (section 4.1.3).[29]

This outcome is consistent with results from clinical trials in which the addition of an LHRH analogue to radiotherapy improved overall survival in men with locally advanced prostate cancer.[6] The addition of goserelin to conventional radiation therapy in this group of patients, and in particular those with node-positive disease, was associated with an increased survival benefit compared with radiation therapy alone.[41,42,44] Men with locally advanced high-grade prostate cancer are more likely to have micrometastatic disease than those with localised disease; consequently, this benefit may be the result of adding systemic therapy to localised radiation therapy.[48] Whether or not the addition of bicalutamide to the other standard therapies will have a beneficial effect on overall survival in men with locally advanced prostate cancer remains to be seen.[49] The likelihood of increased overall survival with bicalutamide approaching statistical significance has been observed in men who otherwise would have been managed by watchful waiting (section 4.1.3).

Although equivalence between bicalutamide monotherapy and surgical or medical castration in

terms of progression-free survival and overall survival could not be established in clinical trials, bicalutamide has a generally better pharmacological tolerability profile than castration therapy. The important HR-QOL issues of sexual interest (which often declines in men with prostate cancer due to the disease itself or its treatment[50]) and physical function were better maintained with bicalutamide than with castration at 12 months after treatment was initiated (section 4.2). In addition, the incidence of hot flushes was lower with bicalutamide than with castration and loss of BMD was avoided (sections 2 and 5), because serum testosterone remains at physiological levels during treatment.[5,39] Bicalutamide has been associated with clinically relevant increases in liver function tests in a small proportion of patients, and periodic monitoring of hepatic function is recommended (section 6); however, these events are usually transient and are rarely severe.

As would be expected with antiandrogen therapy, gynaecomastia and breast pain occurred more frequently in men receiving bicalutamide as adjuvant therapy or monotherapy in the EPC programme and the monotherapy trials than with standard therapy alone or castration, although these events were mostly of mild to moderate severity in affected patients (section 5). European Association of Urology (EAU)[5] and European Society for Medical Oncology[9] guidelines suggest that these symptoms are managed with prophylactic radiation therapy administered prior to commencing bicalutamide; EAU guidelines[5] also recommend use of the antiestrogen tamoxifen or aromatase inhibitors. Low-dose prophylactic radiation therapy is the most frequently used of these treatments; however, there is increasing interest in the use of hormonal treatments.[51]

Recent preliminary studies in men with localised or locally advanced prostate cancer have shown that the addition of tamoxifen,[21,52-54] but not the aromatase inhibitor anastrozole, to bicalutamide adjuvant therapy or monotherapy as prophylaxis or treatment significantly reduces the incidence of bicalutamide-induced gynaecomastia and breast pain,[21,52,53] and that tamoxifen is more effective than radiation therapy.[52,54] A dose-response study examining different prophylactic doses of tamoxifen 1–20 mg/day or placebo administered for 1 year with bicalutamide 150 mg/day found that after 6 months' treatment, a 20 mg/day dosage of tamoxifen was likely to be optimal for reducing bicalutamide-induced breast events and did not appear to affect disease control, as assessed by PSA inhibition (available as an abstract).[55] Further studies are required to confirm this outcome and to evaluate the longer-term potential effects of adding tamoxifen to bicalutamide in such patients, including effects on progression-free and overall survival.[51,53-56]

As with any new therapy, establishing whether bicalutamide provides value for money in the treatment of men with locally advanced prostate cancer is important. Pharmacoeconomic analyses of bicalutamide relative to other available therapies for this group of patients are not currently available, although a cost-effectiveness analysis from a Belgian healthcare payer perspective of adjuvant bicalutamide relative to standard care in early prostate cancer has been published.[57] In this analysis, a Markov model was developed using efficacy and tolerability data from the EPC programme (i.e. data from patients with localised or locally advanced prostate cancer). Further analyses in the subgroup of patients most benefiting from the addition of bicalutamide to standard therapy (i.e. men with locally advanced prostate cancer) are awaited with interest.

In conclusion, bicalutamide administered in conjunction with standard care in men with locally advanced prostate cancer offers disease-free survival benefits over standard care alone and is generally well tolerated. In addition, overall survival is improved to a greater extent when bicalutamide is administered with radiation therapy compared with radiation therapy alone in these patients. Compared with surgical or medical castration, bicalutamide monotherapy offers better tolerability and higher HR-QOL scores for sexual interest and physical capacity in men with locally advanced prostate cancer, while achieving disease-free and overall survival durations that were not significantly different. Thus, when treatment options are being evaluated, bicalutamide as adjuvant therapy or monotherapy should be considered as an alternative to other available hormonal therapies in men with locally advanced prostate cancer, especially in those who wish to maintain an active lifestyle.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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