Bicalutamide treatment for locally advanced prostate cancer

John Anderson

In men with locally advanced prostate cancer, bicalutamide 150mg monotherapy provides a similar disease outcome to medical or surgical castration. However, castration is associated with loss of sexual interest and function, decreased energy and an increased risk of osteoporotic fractures. Bicalutamide 150mg monotherapy has less impact on sexual interest and physical capacity than castration.

The profile of prostate cancer patients is changing from that of mainly elderly men with bone metastases at diagnosis to that of younger, more physically and sexually active men presenting with earlier disease (Kirby, 1998).

When prostate cancer is locally advanced, surgery or radiotherapy alone may not be capable of effecting a cure (Roach, 1997). Many patients will be offered androgen deprivation therapy, traditionally surgical castration or luteinizing hormone-releasing hormone (LHRH) analogue therapy, either alone or together with an antiandrogen as maximal androgen blockade (MAB). However, castration may have a significant impact on the patients' wellbeing because of the psychological effect of surgery and long-term side-effects. Alternative therapies are therefore always welcome, particularly for younger men who are more likely to stay on therapy for a prolonged period.

BICALUTAMIDE

Bicalutamide 150 mg monotherapy is an hormonal option for oral therapy in patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical interventions are not considered appropriate or acceptable. Bicalutamide is a non-steroidal antiandrogen with a long elimination half-life, allowing once-daily administration. A 50 mg formulation has been available for some years for use as a component of MAB for the treatment of advanced metastatic prostate cancer. When used as monotherapy in locally advanced disease, the recommended dose of bicalutamide is 150 mg (Kolvenbag and Nash, 1999).

Non-steroidal antiandrogens are competitive antagonists of the androgen receptor in prostatic cells. The resulting low testosterone levels cause sexual dysfunction, a reduction in energy and muscle mass, and osteoporosis. These side-effects can have a deleterious impact on quality of life, particularly for the younger man. Bicalutamide 150 mg therefore presents several theoretical benefits over castration in respect of quality of life and patient wellbeing. Comparative studies have been conducted to establish if these benefits are realized in clinical practice.

EFFICACY OF BICALUTAMIDE 150 MG MONOTHERAPY IN LOCALLY ADVANCED PROSTATE CANCER

The efficacy of bicalutamide 150 mg in prostate cancer has been compared with castration (medical or surgical) in two large clinical studies, which were identical in design to allow a combined analysis. These randomized studies included patients with locally advanced (n=480) or metastatic (n=805) disease, but as outcome differed by disease stage, the two groups were analysed separately (Tyrrell et al, 1998).

In the locally advanced patients with locally advanced disease, a mature combined analysis (when 56% of the patients had died) at a median follow-up of 6.3 years demonstrated that overall survival did not differ significantly between bicalutamide and castration (*Figure 1*) (Iversen et al, 2000). There was also no statistically significant difference between the groups in time to disease progression (Iversen et al, 2000). Thus, locally advanced patients treated with bicalutamide 150 mg monotherapy can expect a disease outcome that is comparable to that for castration.

Mr John Anderson is Clinical Director of Urology, Royal Hallamshire Hospital, Sheffield S10 2JF

QUALITY OF LIFE BENEFITS OF BICALUTAMIDE 150 MG

Maintaining a good quality of life is increasingly recognized as an important aspect of cancer treatment, and aspects of sexual life are key components of this. Surveys of men in the age range typically affected by prostate cancer have revealed that many would be prepared to trade some survival advantage for preservation of sexual function (Singer et al, 1991; Mazur and Hickman, 1993).

Sexual interest typically declines as a result of the altered aspects of sexual life of men suffering from prostate cancer, either as a consequence of the disease itself or as a result of its treatment (Kirby et al, 1998). The preservation of sexual interest during therapy is important, as treatment for sexual dysfunction is futile in the absence of sexual interest. In the two bicalutamide 150 mg monotherapy studies, the decline in sexual interest was statistically significantly (P=0.029) greater following castration than bicalutamide 150 mg monotherapy (*Figure 2*) (Iversen, 1999). The benefits of bicalutamide 150 mg over castration were apparent within 1 month and continued for the 12-month follow-up period (*Figure 3*). The deterioration in sexual function was less in the bicalutamide 150 mg group compared with castration but the number of men providing data on sexual function was insufficient for statistical analysis (Iversen, 1999).

The assessment of physical capacity in the two monotherapy studies also statistically significantly favoured bicalutamide (P=0.046) (*Figure 2*). This assessment covered aspects of daily living such as walking, climbing stairs, sports, lifting, bending, dressing, bathing/showering, and shopping, some of which would be affected by the loss of energy and muscle mass typically seen after castration (Sih et al, 1997; Iversen et al, 2000). Bicalutamide 150 mg was also favoured with respect to emotional wellbeing, vitality, social function, pain, activity limitation and bed disability (*Figure 2*), although the differences did not achieve statistical significance.

These results indicate that treatment with bicalutamide may have less impact on these patients' lifestyles than castration.

BONE MINERAL DENSITY

Testosterone deficiency caused by surgical or medical castration results in a significant decrease in bone mineral density (BMD) and an increase in osteoporotic fractures (Townsend et al, 1997; Daniell et al, 2000). Hip fractures are associated with considerable morbidity (Cooper, 1997) and have significant quality of life implications for men with locally advanced prostate cancer.

Bicalutamide monotherapy would not be expected to affect BMD as physiological testosterone levels are maintained. This is consistent with the findings from a small subgroup of men (n=29) with locally advanced disease at entry to the two large monotherapy studies (Iversen et al, 2000). Measurements of BMD were determined in patients who had been receiving treatment for a median of 5.5 years and had no evidence of metastatic bone disease. Femoral neck and total hip BMD in bicalutamide 150 mg-treated patients were similar to measurements in age-matched healthy men, whereas BMD in castrated patients was lower than the normal for their age.

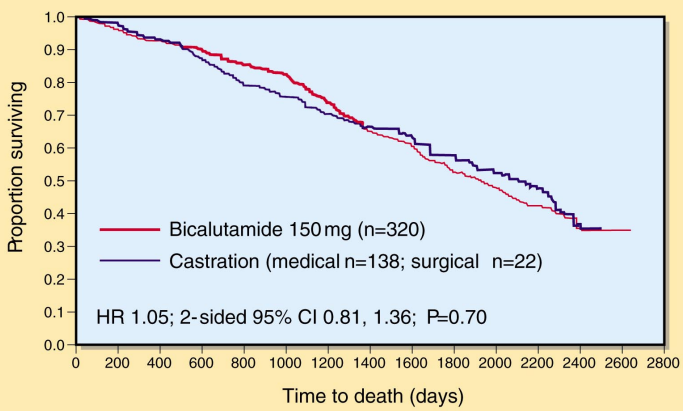

Figure 1. Kaplan–Meier probability of time to death in the bicalutamide 150 mg monotherapy studies. From Iversen et al (2000). CI = confidence interval; HR = hazard ratio.

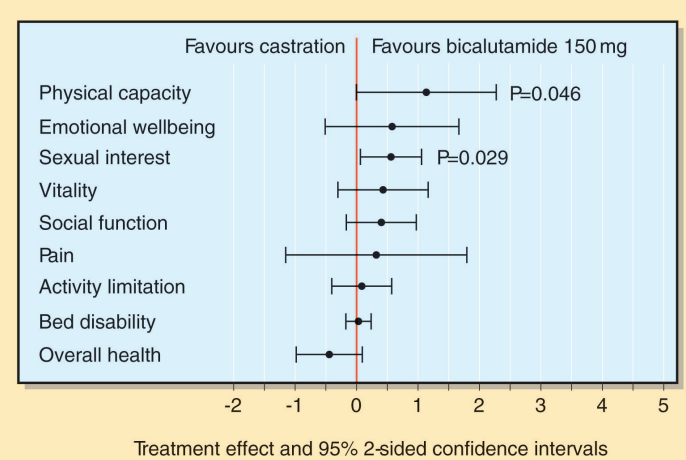

Figure 2. Quality of life analysis at 12 months in the bicalutamide 150 mg monotherapy studies (bicalutamide 150 mg n = 320; medical castration n = 138 and surgical castration n = 22). From Iversen (1999).

Thus, patients who receive bicalutamide 150 mg monotherapy may have a lower risk of osteoporosis and hip fractures than castrated patients.

SIDE-EFFECTS

The side-effect profile of bicalutamide is largely predictable from its pharmacology. During non-steroidal antiandrogen monotherapy, the effects of oestrogens on the breast are unopposed as a result of androgen blockade, and gynaecomastia and breast pain are common side-effects. In the two bicalutamide 150 mg monotherapy studies these breast changes occurred mainly in the first year of treatment (Iversen, 1999) and were more frequent than with castration (Iversen et al, 2000) (*Figure 4*). However, treatment withdrawal was because of breast pain or gynaecomastia was only necessary in 1.3% of patients (Iversen et al, 2000). Prophylactic irradiation can effectively prevent breast changes and therapeutic irradiation may alleviate breast pain, while established gynaecomastia can be treated surgically if desired (Tyrrell, 1999). In addition, patients are more able to tolerate gynaecomastia if there is a full discussion with their doctor early in the treatment decision process about the likelihood of its occurrence.

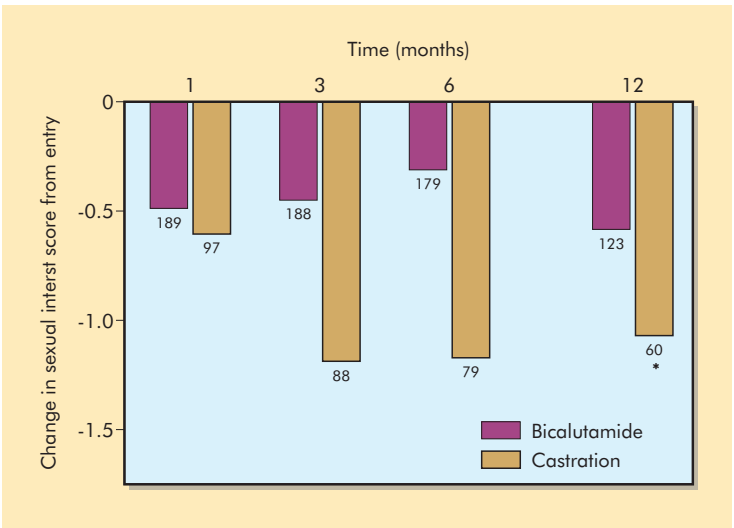

*Figure 3. Changes in sexual interest over time in the bicalutamide 150 mg monotherapy studies (AstraZeneca, data on file 020). *P = 0.029, the difference in least squares means at 12 months.*

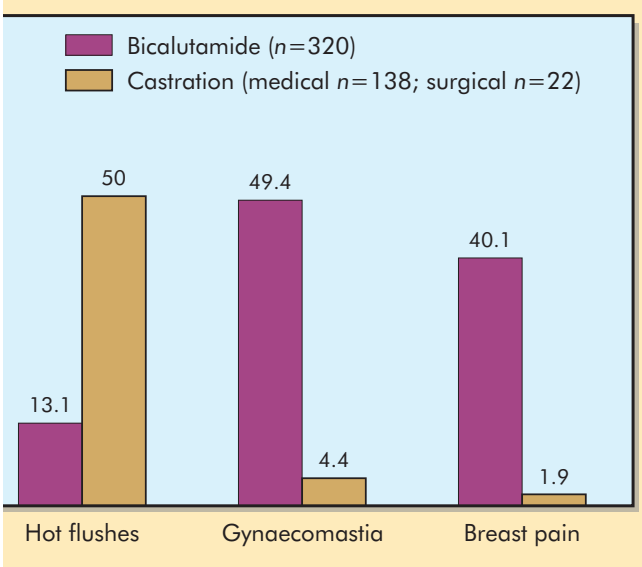

Figure 4. Pharmacological effects of bicalutamide 150 mg and castration in the bicalutamide 150 mg monotherapy studies (Iversen et al, 2000).

Hot flushes, a frequent and often distressing consequence of the low testosterone levels after castration (Buchholz and Mattarelli, 1994), are less common with bicalutamide monotherapy (Iversen et al, 2000) (*Figure 4*).

It should be noted, however, that terfenadine, astemizole and cisapride are contraindicated with bicalutamide 150 mg. Caution should be exercised when co-administering with cyclosporin and calcium-channel blockers, with drugs metabolized predominantly by CYP 3A4 and drugs which may inhibit drug oxidation, e.g. cimetidine and ketoconazole.

The incidence of non-pharmacological side-effects with bicalutamide monotherapy is comparable to castration. Overall, bicalutamide 150 mg is well tolerated; in the two large bicalutamide 150 mg monotherapy studies, only 4.1% of patients withdrew because of drug-related events (Iversen et al, 2000).

INDICATIONS FOR BICALUTAMIDE 150 MG MONOTHERAPY

Treatment decisions for men with locally advanced prostate cancer are best individualized, taking into account the risks and benefits of the available treatment options. Many men will be worried about the impact of castration on their quality of life. Additionally, some men may prefer an oral therapy, have personal reasons for avoiding castration or be unable to tolerate LHRH analogue therapy. Bicalutamide 150 mg monotherapy may be offered to patients with locally advanced prostate cancer in whom castration is inappropriate or unacceptable (*Table 1*).

CONCLUSION

The availability of bicalutamide 150 mg monotherapy widens the treatment options for men with locally advanced prostate cancer. Bicalutamide 150 mg provides a similar survival outcome to castration, but confers statistically

TABLE 1.
Indications for bicalutamide 150 mg monotherapy in locally advanced prostate cancer

Patients who may be considered for bicalutamide 150 mg monotherapy:	Those for whom castration poses unacceptable risks
	Those who are intolerant to luteinizing hormone-releasing hormone analogues
	Those who have cultural reasons for refusing castration
	Those who cannot tolerate the psychological impact of castration
	Those for whom other medical interventions are not appropriate
	Those who wish to maintain sexual interest and function
	Those for whom retention of physical capacity is important

significant benefits in the quality of life domains of physical capacity and sexual interest. Additionally, preliminary data indicate that BMD is maintained. HM

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KEY POINTS

- Bicalutamide 150 mg is an oral therapy that can be administered once daily.
- In men with locally advanced prostate cancer, bicalutamide 150 mg monotherapy provides a similar disease outcome to medical or surgical castration.
- Many men with locally advanced prostate cancer are physically and sexually active at the time of diagnosis.
- Castration, whether achieved surgically or medically, is associated with loss of sexual interest and function, decreased energy and an increased risk of osteoporotic fractures.
- Bicalutamide 150 mg monotherapy has less impact on sexual interest and physical capacity than castration.
- Bicalutamide 150 mg monotherapy is well tolerated. The principal side-effects are gynaecomastia and breast pain, which can be managed by prophylactic or therapeutic radiotherapy or surgery and the patient being fully informed about the condition.
- Preliminary results indicate that bone mineral density is less affected by bicalutamide 150 mg monotherapy than castration.
- Bicalutamide 150 mg monotherapy is an alternative treatment option to castration in patients with locally advanced non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable.