CONFLICT OF INTEREST

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Abbreviations: **3D**, three-dimensional.

THE ROLE OF TAMOXIFEN IN REDUCING BICALUTAMIDE-INDUCED GYNAECOMASTIA AND BREAST PAIN

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INTRODUCTION

Gynaecomastia and breast pain are troublesome side-effects often experienced by men receiving hormonal therapy for prostate cancer [1]. Bicalutamide (Casodex™, AstraZeneca) is a nonsteroidal antiandrogen used in the treatment of prostate cancer, particularly in men trying to avoid some of the consequences of castration. The most common side-effects attributed to bicalutamide are gynaecomastia and breast pain, which are reported in over half of patients [2,3]. Gynaecomastia and breast pain often resolve on cessation of bicalutamide, but this might depend on the duration of therapy, as in one study gynaecomastia resolved in 64% of those taking bicalutamide for <6 months, but in only 29% of those taking it for >18 months [2]. This might be explained by the development with time of irreversible fibrotic changes within the breast tissue. Prophylactic breast irradiation has been used successfully to treat antiandrogen-induced gynaecomastia. For instance, in one study the incidence of gynaecomastia in men taking an antiandrogen for locally advanced prostate cancer treated with radiation was 28%, compared to 71% in those who did not receive radiation [4].

The development of gynaecomastia is thought to relate to an imbalance in the ratio between oestrogens and androgens, although in many cases the cause is often unknown and in others might be associated with a degree of hypogonadism [1]. The increased testosterone levels usually seen in men on antiandrogen monotherapy are thought to be the reason for the development of gynaecomastia. These can lead to a rise in the level of 17β-oestradiol secondary to androgen aromatization. These elevated oestrogen levels cause an irreversible benign proliferation of male breast tissue, perpetuated by the blockade of inhibitory androgen activity at the breast-bud [5]. Disrupting this process provides a rationale for preventing bicalutamide-induced breast pain or gynaecomastia, either by directly blocking the effect of oestrogen at a cellular level or by interfering with the peripheral aromatization of testosterone. Preliminary data showing a role for tamoxifen (Nolvadex-D™, AstraZeneca) in treating hormone-induced gynaecomastia and breast tenderness were first published in 1997 [6]. More recently, several randomized studies examined the effect of tamoxifen, an anti-oestrogen, and anastrozole (Arimidex™, AstraZeneca), a selective aromatase inhibitor, in preventing these side-effects.

Boccardo *et al.* [7] randomized 114 men with either localized, locally advanced or biochemically recurrent prostate cancer to bicalutamide plus either placebo, tamoxifen (20 mg/day) or anastrozole (1 mg/day) for 48 weeks. The endpoints of the study were the incidence of breast pain and gynaecomastia, serum PSA level, and sexual functioning scores. They found that the incidence of gynaecomastia was 73%, 10% and 51% in the placebo, tamoxifen and anastrozole groups, respectively; similarly, the respective incidence of breast pain was 39%, 6% and 27%. Adverse effects occurred in 37%, 35%

and 69% of the patients, respectively, but there was no difference between the groups in sexual functioning. The baseline PSA level decreased by ≥50% in 97%, 97% and 83% of the three groups, respectively. The authors concluded that tamoxifen, unlike anastrozole, was effective in reducing bicalutamide-induced gynaecomastia in the short term. Furthermore, they suggested that tamoxifen might be beneficial in treating gynaecomastia, as three of the five patients randomized to the tamoxifen group who had gynaecomastia at the start of the trial improved by the end of it.

In another trial, Saltzstein *et al.* [8] randomized 107 men receiving bicalutamide after radical treatment for prostate cancer to either tamoxifen (20 mg/day), anastrozole (1 mg/day) or placebo for 3 months. The incidence of gynaecomastia and/or breast-pain was 11.8% in the tamoxifen group compared with 63.9% and 69.4% for the anastrozole and placebo groups, respectively. However, the benefits of tamoxifen did not persist upon withdrawal in about three-quarters of cases, but on re-treatment with tamoxifen if symptoms arose, it was effective in about two-thirds of cases. Moreover, cancer control assessed by PSA levels showed no difference between each arm of the study.

Di Lorenzo *et al.* [9] randomized 102 men receiving adjuvant bicalutamide after radical prostatectomy for either localized or locally advanced prostate cancer into three groups. The first group received only bicalutamide, the second group also received tamoxifen (10 mg/day) for 24 weeks, and the third group received a single dose of prophylactic breast irradiation (12 Gy) in addition to the bicalutamide. Furthermore, men in group 1 who developed gynaecomastia or breast pain were then randomized to either tamoxifen or radiotherapy. The minimum follow-up was 12 months and the incidence of gynaecomastia was 67%, 8% and 34% in the three groups, respectively. Similarly, breast pain was more common in group 1 than in the other groups (58%, 7% and 30%, respectively). In men from group 1 who developed gynaecomastia or breast pain, tamoxifen was a more successful therapy than radiation. There were no apparent differences among the three groups in PSA relapse-free survival. The authors concluded that tamoxifen was a more effective treatment than radiation for preventing bicalutamide-induced gynaecomastia.

These recent studies suggest that bicalutamide-induced gynaecomastia and breast pain might not only be prevented by tamoxifen but, in some patients, also treated. Tamoxifen performed better than radiation with no increase in adverse events. Anastrozole did not appear to be effective. The optimum dose of tamoxifen used in either the prophylaxis or treatment of gynaecomastia or breast pain remains to be determined. Most studies have used a dose of 20 mg/day as this is the dose licensed for early breast cancer, but daily doses of 10–40 mg have been used with similar results. It is unclear as to the optimum duration patients should remain on tamoxifen once starting bicalutamide therapy. However, the cost of taking tamoxifen (20 mg/day) is not great, it being estimated at UK £26 (€38; US $48) for 3 months and £104 (€152; $192) for a year [10]. Based on the data in these studies, the 'number needed to treat' to prevent one episode of gynaecomastia and/or breast pain using tamoxifen compared with placebo varied from ≈1.6 to 3.0. Similarly, for radiation the 'number needed to treat' varied from 2.3 to 3.6. The long-term effects of tamoxifen on prostate cancer progression or mortality remain to be seen, but in the short-term at least, do not seem to be adversely affected. Given these results, if tamoxifen proves to be safe in the longer-term, there would appear to be no disadvantage in using tamoxifen instead of radiotherapy. In which case, the choice of one method over another would be driven by patient preference, known toxicities and local logistics [11].

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