Management of breast side-effects in men treated with androgen deprivation therapy

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In this series, the authors present cases of men being treated with androgen deprivation therapy, and highlight management strategies to prevent and treat associated toxicities. In this third article, the authors consider the management of gynaecomastia and mastalgia.

THE CASE

A 61-year-old man with a strong family history of prostate cancer had a routine prostate-specific antigen (PSA) blood test, which measured 29ng/ml. Staging investigations revealed T3b N0 M0 adenocarcinoma of the prostate. On biopsy, the Gleason score was 4+4 in 7/12 cores with a maximum core tumour length of 100 per cent. The patient was otherwise in good health, with no past medical history of note, and he was not on any medications.

The treatment plan, after discussion at the multidisciplinary team meeting, was for three months of neoadjuvant luteinising hormone-releasing hormone (LHRH) agonist, followed by radical radiotherapy. This was to be followed by three years of an adjuvant antiandrogen, bicalutamide 150mg once daily. The side-effects of bicalutamide, including gynaecomastia and mastalgia, were discussed with the patient.

INCIDENCE OF BREAST SYMPTOMS

Bicalutamide 150mg is a non-steroidal antiandrogen, which can be used in locally advanced prostate cancer as an alternative to castration-based therapy with LHRH agonists. Bicalutamide 150mg has some potential advantages over castration-based therapy in that it has been shown to maintain physical capacity and bone mineral density and has a reduced risk of hot flushes and loss of sexual function and interest. This is, however, at the expense of an increased risk of gynaecomastia and mastalgia. Bicalutamide 150mg has hypergonadotrophic effects and androgens are aromatised in extragonadal tissues to 17β-oestradiol, which induces the benign proliferation of breast tissues and causes gynaecomastia, and associated breast pain during the proliferative phase.

The Early Prostate Cancer Study was a large prospective randomised study of 8113 men, looking at the efficacy and tolerability of bicalutamide 150mg once daily, both as a monotherapy and adjuvant to radical radiotherapy and radical prostatectomy in patients with locally advanced disease. The 10-year analysis reported that gynaecomastia and breast pain occurred in 69 and 73 per cent of patients receiving bicalutamide 150mg respectively; 16 per cent of patients discontinued treatment because of this, highlighting the need for prophylaxis in some patients.

Gynaecomastia and mastalgia (swollen and painful breasts) are potential unwanted side-effects for patients who are treated with hormone therapy for prostate cancer (Figure 1). The incidence of breast symptoms varies with different types of therapy and has been reported in 13 per cent of men on LHRH agonists and 70 per cent of those having therapy with an antiandrogen such as bicalutamide 150mg or oestrogens.

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PROPHYLAXIS AGAINST GYNAEOMASTIA AND MASTALGIA

Current NICE guidelines state that ‘men starting long-term bicalutamide 150mg monotherapy (>six months) should receive prophylactic radiotherapy to both breast buds within the first month of treatment. A single fraction of 8Gy using orthovoltage or electron beam radiotherapy is recommended’.3

Prophylactic breast irradiation is commonly used for men prior to commencing stilboestrol therapy for advanced prostate cancer in the palliative setting. However, bicalutamide 150mg is licensed for men with locally advanced disease and can be prescribed as monotherapy or as adjuvant treatment in combination with radical radiotherapy to the prostate or with salvage postoperative, prostate bed radiotherapy. In these groups of patients there are different therapy intentions and also a much longer anticipated survival to those being treated with stilboestrol for advanced metastatic castration-resistant prostate cancer. The use of prophylactic breast irradiation to attempt to prevent gynaecomastia and mastalgia with bicalutamide 150mg therefore causes concern regarding the long-term effects of treating a benign condition with radiation, especially with regards to the risk of long-term second malignancy in men who may otherwise be ‘cured’ of or in remission from their prostate cancer.

The efficacy of prophylactic breast bud radiotherapy in the prevention of gynaecomastia and breast pain in patients being treated with bicalutamide has been evaluated in a randomised, sham-controlled double-blind trial.4 One hundred and six patients were randomised to receive a 10Gy single fraction of breast bud radiotherapy or sham radiotherapy prior to commencing bicalutamide 150mg daily. A reduction in both investigator- and patient-assessed gynaecomastia was demonstrated in favour of the prophylactic radiotherapy group (51.9 versus 85.2 per cent, p<0.001; 50 versus 81 per cent, p<0.01). There was a small decrease in breast pain in the radiotherapy group but this did not reach statistical significance. Acute toxicities were transient and well tolerated. Late effects were not accounted for. Although this study showed a modest but significant reduction in breast swelling, half of the men treated with radiotherapy still complained of a degree of breast swelling and there was no significant reduction in mastalgia.

There are very little data regarding late effects of radiotherapy; however, cases have been reported of second malignancy following prophylactic radiotherapy, and this does pose a theoretical risk.5

ALTERNATIVE TREATMENTS

Alternative treatments have been investigated as prophylaxis for these patients. These include exploiting the anti-oestrogenic effects of drugs such as tamoxifen, although it is not licensed for this indication.

One multicentre prospective trial6 randomised post-prostatectomy patients between bicalutamide, bicalutamide plus tamoxifen, and bicalutamide plus breast bud radiotherapy (12Gy). Patients in the first group who developed gynaecomastia or mastalgia were then further randomised to receive tamoxifen or radiotherapy. This study demonstrated that tamoxifen was more effective than radiotherapy at preventing and treating gynaecomastia and breast pain; there was no associated reduction in quality of life, erectile dysfunction or PSA relapse.

In another study, Boccardo et al.7 randomised 114 patients to receive placebo, tamoxifen or anastrazole before bicalutamide 150mg therapy. They reported a significant reduction in gynaecomastia in the tamoxifen group, but not the anastrazole group (control group, 73 per cent gynaecomastia; tamoxifen group, 10 per cent; anastrozole group, 51 per cent; p<0.001). A significant reduction in breast pain was also seen in the tamoxifen group only (39 versus 6 per cent), but no significant difference was seen in the anastrozole group. There was no significant difference between the groups for...
achieving a >50 per cent PSA reduction or for serious adverse events, quality of life, libido and sexual function.

Patients who develop persistent gynaecomastia in spite of prophylaxis, or who have not taken prophylactic measures, then have the option of surgery. Surgical procedures include adnomammectomy with periareolar incision, or incision and liposuction. Complications include seroma, bleeding, poor cosmetic outcome, need for revision and general anaesthetic complications. One series of 126 patients having surgery for all causes of gynaecomastia found a complication rate of 17 per cent and a patient satisfaction rate of 8.2/10.

CONCLUSION
In conclusion, we have presented a case of a patient with locally advanced prostate cancer who is about to embark on three years of adjuvant antiandrogen therapy (bicalutamide 150mg). We have raised the issue of the potential complication of gynaecomastia and mastalgia and would wish to discuss prophylactic measures with the patient. The efficacy of breast bud radiotherapy is equivocal and comes with the inconvenience of having to attend for radiotherapy, and the late effects, including second malignancy, have not been quantified in the literature. As we would expect this patient to have a significant chance of long-term disease control, greater consideration needs to be made to minimise the risk of serious late effects.

Declaration of interests
Heather Payne has attended and received honoraria for advisory boards and served as a consultant for Teva, Astra Zeneca, Janssen, Johnson and Johnson, Sanofi Aventis, Takeda, Ferring and Novartis.

REFERENCES