Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial

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Summary

Background Gynaecomastia and breast pain are frequent adverse events with bicalutamide monotherapy, and might cause some patients to withdraw from treatment. We aimed to compare tamoxifen with radiotherapy for prevention and treatment of gynaecomastia, breast pain, or both during bicalutamide monotherapy for prostate cancer.

Methods 51 patients were randomly assigned to 150 mg bicalutamide per day, 50 patients to 150 mg bicalutamide per day and to 10 mg tamoxifen per day for 24 weeks, and 50 patients to 150 mg bicalutamide per day and radiotherapy (one 12-Gy fraction on the day of starting bicalutamide). 35 of the 51 patients allocated bicalutamide alone developed gynaecomastia or breast pain and were subsequently randomly allocated to tamoxifen (n=17) or radiotherapy (n=18) soon after symptoms started (median 180 days, range 160–195). Gynaecomastia and breast pain were assessed once a month. Severity of gynaecomastia was scored on the basis of the largest diameter. Breast pain was scored as none, mild, moderate, or severe. The primary outcome was frequency of gynaecomastia or breast pain; secondary outcomes were safety and tolerability, relapse-free survival, as assessed by concentration of prostate specific antigen, and quality of life. Analyses were by intention to treat.

Results 35 of 51 patients assigned bicalutamide alone developed gynaecomastia, compared with four of 50 assigned bicalutamide and tamoxifen (odds ratio [OR] 0·1 [95% CI 0·08–0·12], p=0·0009), and with 17 of 50 assigned bicalutamide and radiotherapy (0·51 [0·47–0·54], p=0·008). Breast pain was seen in 29 of 51 patients allocated bicalutamide alone, compared with three allocated bicalutamide and tamoxifen (0·1 [0·07–0·11], p=0·009), and with 15 allocated bicalutamide and radiotherapy (0·43 [0·40–0·45], p=0·02) In 35 patients assigned bicalutamide alone who subsequently developed gynaecomastia, breast pain, or both, tamoxifen significantly reduced the frequency of gynaecomastia (0·2 [0·18–0·22], p=0·02).

Interpretation Antioestrogen treatment with tamoxifen could help patients with prostate cancer to tolerate the hypergonadotropic effects of bicalutamide monotherapy.

Introduction

The progression of prostate cancer is a continuum through four main stages of localised, locally advanced, metastatic, and hormone-refractory disease.[1] Treatment options with curative intent for early stages include radical prostatectomy and radiotherapy, and many men who receive early treatment have an excellent outcome. However, many men have disease recurrence,[2] measured by an increased concentration of prostate specific antigen (PSA), which is generally considered to be the earliest evidence of persistent or recurrent disease after primary treatment with curative intent.[3]

Bicalutamide is a potent, well tolerated non-steroidal antiandrogen. In previously untreated patients with non-metastatic prostate cancer, 150 mg bicalutamide was equal to castration in terms of survival after a median follow-up of 6·3 years, and had benefit with regard to sexual interest and physical capacity.[4] Two smaller European comparisons of 150 mg bicalutamide with complete androgen blockade confirmed these findings.[5,6]

The benefit of adding 150 mg bicalutamide per day to standard care for patients with early prostate cancer is being investigated in the bicalutamide early prostate cancer (EPC) programme, which consists of three multicentre trials of 8113 patients worldwide with localised or locally advanced prostate cancer. At a median follow-up of 5·4 years, analyses have shown a clinical benefit for bicalutamide in patients with locally advanced disease. The EPC programme is continuing, and data for the effect of bicalutamide on mortality are awaited. Moreover, follow-up data will clarify further the role of bicalutamide in this setting.[7] To date, monotherapy with 150 mg bicalutamide has not been approved by the US Food and Drug Administration, but has been licensed in some European countries as adjuvant treatment for early prostate cancer.

Gynaecomastia, with or without breast pain, is a frequent adverse event of treatment with non-steroidal antiandrogens, and arises from an increase in the ratio of effective oestrogen to androgen in the breast as a result of hypergonadotropic effects of the drugs.[8] In the

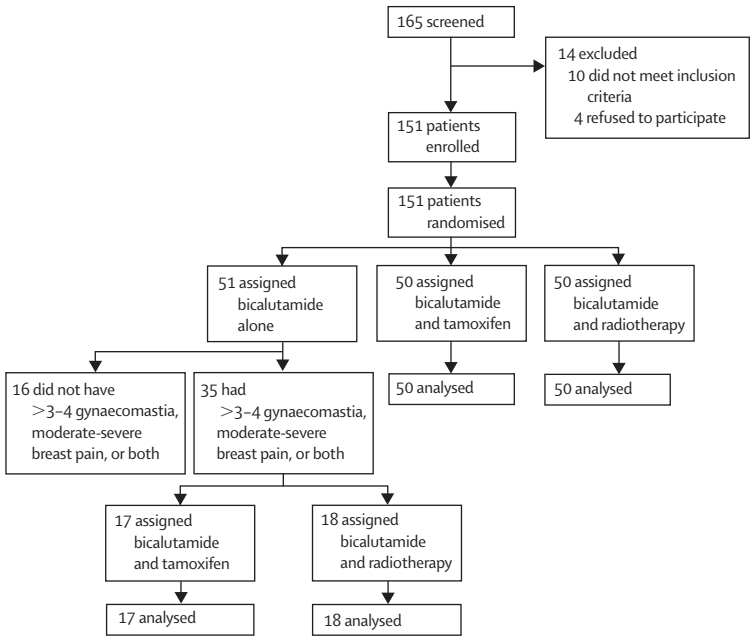

Figure 1: Trial profile

EPC programme, 2747 (68%) of 4022 patients developed gynaecomastia and 2960 (74%) developed breast pain, and symptoms developed mostly in the first 6–9 months of bicalutamide treatment. Although these events were mostly mild and moderate, 671 (17%) patients have been withdrawn from the programme because of gynaecomastia, breast pain, or both.[7]

Because early withdrawal from treatment with 150 mg bicalutamide might compromise outcome, effective management strategies for gynaecomastia and breast pain are needed. Controlled trials have shown the efficacy of prophylactic antioestrogen treatment and prophylactic breast irradiation for gynaecomastia and breast pain caused by bicalutamide monotherapy.[8,9]

We aimed to compare the efficacy of tamoxifen with that of electron-beam radiotherapy for the prevention and treatment of gynaecomastia and breast pain caused by monotherapy with 150 mg bicalutamide for prostate cancer.

	Bicalutamide alone (n=51)	Bicalutamide and tamoxifen (n=50)	Bicalutamide and radiotherapy (n=50)
Age (years)			
Median (range)	68·5 (50·2–77·3)	67·5 (57·3–76·1)	70·5 (50·0–74·2)
Stage			
T1–2	35	32	34
T3	15	16	15
T4	1	2	1
Median Gleason score			
<7	29	28	27
⩾7	22	22	23
Median PSA before primary treatment (mg/L)			
<10	30	30	31
⩾10	21	20	19
Node status			
Positive	3	4	3
Negative	35	33	32
Unknown	13	13	15
Primary treatment			
Surgery	35	36	34
Radiotherapy	16	14	16

Table 1: Baseline characteristics

Methods

Patients

We did a randomised trial in five Italian Centres between January, 2002, and February, 2004. The study consisted of men who had histologically confirmed prostate cancer, no distant metastases (ie, T1–T4, any N, and M0), and no evidence of current gynaecomastia or breast pain. All patients had had primary treatment with curative intent (ie, radical prostatectomy or radiotherapy). All 151 patients enrolled had breast examinations, laboratory and eligibility assessments, and completed quality-of-life questionnaires.

Exclusion criteria were: previous hormonal treatment for prostate cancer; metastatic disease; evidence of biochemical relapse after primary treatment; haematological (haemoglobin ⩽100 g/L, white-cell count $<3\times10^9$ cells/L, and platelet count $<100\times10^9$ cells/L), renal (creatinine >115 mmol/L), or hepatic (transaminases and bilirubin concentrations ⩾50% normal value) dysfunction; or any comorbidity that could contraindicate use of the trial drugs.

Figure 1 shows the trial profile. Treatment was assigned on a 1:1:1 ratio: 51 patients were randomly assigned to 150 mg bicalutamide (Casodex® 150, AstraZeneca, Milan, Italy) only; 50 patients to 150 mg bicalutamide per day and 10 mg tamoxifen (Nolvadex® 10, AstraZeneca, Milan, Italy) per day for 24 weeks; and 50 patients to 150 mg bicalutamide per day and 12 Gy radiotherapy given in one dose on the same day of starting bicalutamide treatment. Patients assigned bicalutamide alone who subsequently had gynaecomastia or moderate–severe breast pain that was higher than grade 3 were randomly allocated to 150 mg bicalutamide per day and 10 mg tamoxifen per day for 24 weeks or to 150 mg bicalutamide per day and 12 Gy radiotherapy given in one fraction on the day of starting bicalutamide.

Radiotherapy was given as an electron beam directed to a 5-cm diameter of tissue centred around each nipple, and was designed to deliver a minimum dose of 90% between the skin and the chest wall. An appropriate electron energy of 6–12 MeV was selected to cover the depth of tissue. The dose regimen was devised after consultation with a panel of radiotherapists who had expertise in prostate cancer and breast radiotherapy.

Randomisation was done centrally by A Gallo and L Gallo (Pascale Cancer Institute, Naples, Italy) by use of

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a stratified permuted randomisation algorithm that was balanced within institutions. The trial was unblinded. Stratification factors included: primary treatment (surgery *vs* radiotherapy); stage (T1–T2 *vs* T3 *vs* T4); node involvement (positive *vs* negative *vs* unknown); Gleason score (<7 *vs* ≥7); PSA (<10 mg/L *vs* ≥10 mg/L). All randomly assigned patients were included in the efficacy and safety analyses. The primary outcome was frequency of gynaecomastia or breast pain; secondary outcomes were safety and tolerability, relapse-free survival as assessed by PSA concentration, and quality of life. Analysis was by intention to treat.

The trial was done in accordance with the Declaration of Helsinki (1964) as amended in Hong Kong (1989). Each patient gave written informed consent, and the protocol was approved by the ethics committee of every participating centre.

Follow-up assessments

Physical examination and assessments of haematology and serum biochemistry (including total PSA) were done at baseline and every 3 months for at least 12 months. Abdominal ultrasonography, CT, bone scan, and chest radiography were done at baseline to exclude the presence of distant metastases or obvious pelvic disease. Radiological assessments were repeated when disease progression was suspected on the basis of PSA measurement. PSA progression was defined as two consecutive increases in PSA of greater than 0·04 mg/L.

Gynaecomastia and breast pain were assessed once a month. We measured gynaecomastia with callipers, the severity of which was scored on the basis of the largest diameter: grade 1 (≤2 cm); grade 2 (from 2 cm to ≤4 cm); grade 3 (from 4 cm to ≤6 cm); and grade 4 (>6 cm). Breast pain was assessed by questioning the patient at each visit, and severity was scored as none, mild, moderate, or severe.

Quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), which scores physical, role, emotional, cognitive, and social function, and overall health status. It also has multi-item scales and single items that assess various physical symptoms (eg, fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance, loss of appetite, constipation, and diarrhoea). Items are scored from 1 to 4 (rated by the patient who completes the questionnaire as: 1 "not at all"; 2 "a little"; 3 "quite a bit"; and 4 "very much"), apart from items in the overall quality-of-life scale, which range from 1 ("very poor") to 7 ("excellent"). Raw questionnaire scores were transformed into a 100-point scale. For functional scales, high scores represented a high level of functioning; for physical symptoms high scores represent a high level of symptoms or difficulties.[10] Questionnaires were administered at baseline and every 3 months during treatment.

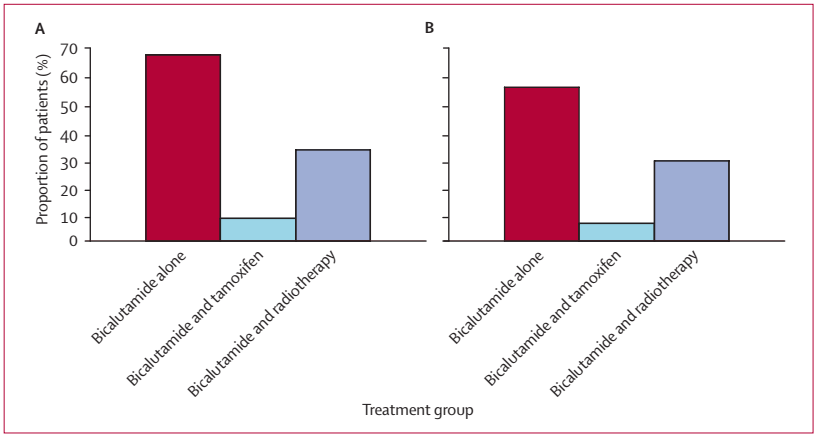

Figure 2: **Grade 3–4 gynaecomastia (A) and moderate-severe breast pain (B) after 6 months**

Statistical analysis

Because gynaecomastia was seen in more than 50% of patients given bicalutamide monotherapy in a previous trial,[7] we defined tamoxifen or radiotherapy as effective if either tamoxifen or radiotherapy combined with bicalutamide decreased the expected frequency of gynaecomastia by more than 50%. Under these conditions, about 50 patients per group were needed to detect such an effect with a power of 80% and a significance level of 5%. The χ^2 test and Fisher's exact test were used to compare the frequency of gynaecomastia, breast pain, adverse effects, and quality of life between groups.[11] PSA relapse-free survival was estimated with the Kaplan-Meier product-limit method. All hypothesis tests were two-sided.

Role of the funding source

This trial was developed between the participants' institutions of Pascale Institute, Federico II University,

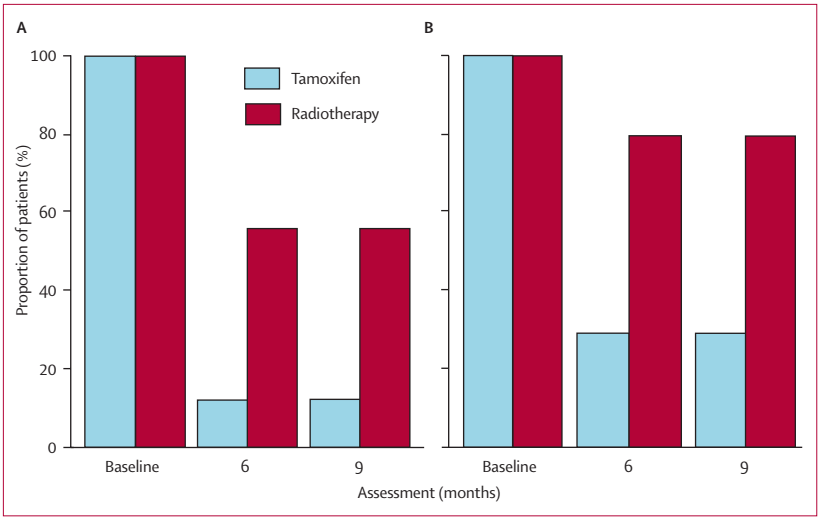

Figure 3: **(A) Grade 3–4 gynaecomastia in 35 patients assigned bicalutamide alone who developed gynaecomastia or breast pain and who were subsequently assigned to tamoxifen or radiotherapy. (B) Breast pain in 29 patients assigned bicalutamide alone who developed concomitant moderate-severe breast pain and who were subsequently assigned to tamoxifen or radiotherapy**

	Bicalutamide alone (n=51)	Bicalutamide and tamoxifen (n=50)	Bicalutamide and radiotherapy (n=50)
Rash/nipple erythema	2	2*	19*
Skin irritation	0	0*	19*
Pruritis	1	4	2
Anaemia	0	1	0
Fever	0	1	1
Myelotoxicity	1	0	2
Asthenia	2	2	5
Cardiovascular events	2	3	2
Neurological events	1	2	1
Constipation	4	5	4
Diarrhoea	3	4	2
Hot flushes	3	3	2

*Significant difference between groups for radiotherapy-associated side-effects (p=0·01).

Table 2: **Side-effects**

Naples, Italy; Second University of Naples, Naples, Italy; and University of Catanzaro, Cantanzaro, Italy. All authors had full access to the data, and the corresponding author had the final decision to submit the paper for publication.

Results

151 patients were randomised and included in analyses (figure 1). Table 1 shows baseline characteristics. Median follow-up was 25 months (range 12–35 months). Figure 2 shows the frequency of grade 3–4 gynaecomastia and moderate-severe breast pain after 6 months. 35 of 51 patients assigned bicalutamide alone developed gynaecomastia, compared with four of 50 assigned bicalutamide and tamoxifen (odds ratio [OR] 0·1 [95% CI 0·08–0·12], p=0·0009), and with 17 of 50 assigned bicalutamide and radiotherapy (0·51 [0·47–0·54], p=0·008). 29 of 51 patients allocated bicalutamide alone developed breast pain, compared with three of 50 allocated bicalutamide and tamoxifen (0·1 [0·07–0·11], p=0·009), and with 15 of 50 allocated bicalutamide and radiotherapy (0·43 [0·40–0·45], p=0·02).

The 35 patients allocated bicalutamide alone who developed gynaecomastia, breast pain, or both were subsequently randomly assigned tamoxifen (n=17) or radiotherapy (n=18). In this subgroup, tamoxifen significantly reduced the frequency of gynaecomastia (OR 0·2, [0·18–0·22], p=0·02). After 6 months and 9 months, gynaecomastia was recorded in two of 17 patients allocated tamoxifen compared with ten of 18 allocated radiotherapy (figure 3). 29 of these 35 patients developed concomitant gynaecomastia and breast pain, and a higher reduction in pain was recorded in the tamoxifen group than in the radiotherapy group (0·35 [0·33–0·38, p=0·045]). After 6 months and 9 months, breast pain was reported in four of 14 patients assigned tamoxifen compared with 12 of 15 assigned radiotherapy (figure 3).

Treatments were well tolerated in the three groups (table 2). All radiotherapy-associated adverse events resolved and were of short duration (median 4·0 weeks, range 2·5–5·2). Patients assigned bicalutamide and radiotherapy had more asthenia than did those in other groups, whereas those assigned bicalutamide and tamoxifen had more constipation, diarrhoea, and pruritis, although these differences were not significant. Figure 4 shows overall quality-of-life scores, and table 3 shows quality-of-life scores for individual scales for the tamoxifen and radiotherapy groups.

Findings from PSA measurements show that, overall, 132 of 151 patients were disease free at a median follow-up of 25 months. Groups did not differ in relapse-free survival: six patients assigned bicalutamide alone, six assigned bicalutamide and tamoxifen, and seven assigned bicalutamide and radiotherapy had a relapse as measured by PSA increase.

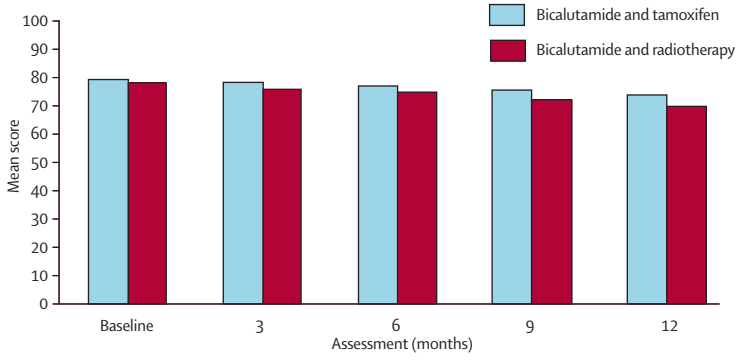

Figure 4: **EORTC QLQ-C30 overall quality-of-life scores in patients assigned tamoxifen or radiotherapy**

Discussion

We have shown that antioestrogen treatment with tamoxifen was more effective than was radiotherapy in preventing the development of bicalutamide-induced gynaecomastia and breast pain in patients with prostate cancer. Moreover, we found that tamoxifen combined with bicalutamide did not increase adverse events and did not compromise quality of life and PSA relapse-free survival compared with bicalutamide alone. To our knowledge, no randomised comparisons of radiotherapy and hormone treatment for the treatment and prevention for bicalutamide-induced gynaecomastia and breast pain have been reported.

The EPC trial programme has reported progression-free survival benefits with immediate 150 mg bicalutamide given in addition to standard care (ie, radical prostatectomy, radiotherapy, or watchful waiting), compared with standard care alone in patients with localised and locally advanced prostate cancer.[7] Gynaecomastia and breast pain are commonly reported adverse events with bicalutamide monotherapy, and cause some patients to withdraw from treatment. Several preventive interventions have been used including surgery, hormone therapy, and radiotherapy,[8]

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	Bicalutamide and tamoxifen					Bicalutamide and radiotherapy				
	Baseline	3 months	6 months	9 months	12 months	Baseline	3 months	6 months	9 months	12 months
Functional scales										
Physical	84·3 (8·1)	80·2 (7·7)	78·2 (7·8)	78·0 (7·8)	77·4 (7·5)	84·0 (7·2)	83·2 (6·9)	83·1 (6·2)	78·4 (6·4)	77·3 (6·9)
Role	77·2 (7·4)	77·0 (7·2)	76·5 (6·9)	76·7 (6·8)	76·1 (6·6)	76·9 (6·1)	75·8 (5·9)	75·3 (6·0)	75·0 (6·1)	74·6 (6·8)
Emotional	79·6 (6·7)	80·0 (6·7)	80·5 (7·2)	80·7 (6·9)	82·3 (6·7)	79·4 (7·2)	79·0 (6·9)	79·2 (6·5)	78·3 (6·8)	78·1 (7·0)
Cognitive	88·5 (7·1)	88·9 (6·8)	90·3 (6·5)	90·1 (7·2)	89·8 (6·5)	88·9 (7·1)	88·0 (7·5)	87·8 (6·7)	88·0 (6·9)	88·7 (6·4)
Social	75·4 (6·6)	76·0 (6·3)	76·5 (6·9)	76·6 (6·4)	76·8 (7·2)	75·8 (6·6)	75·9 (5·7)	75·1 (5·9)	74·2 (6·1)	73·3 (6·6)
Symptom scales										
Fatigue	25·3 (4·0)	23·2 (4·1)	22·1 (3·4)	22·2 (4·2)	22·0 (4.0)	25·0 (3·2)	24·6 (3·6)	23·8 (2·9)	24·2 (3·4)	25·1 (3·3)
Pain	18·2 (5·4)	17·6 (5·5)	18·7 (5·2)	19·1 (4·8)	19·4 (4.7)	18·0 (4·4)	17·3 (4·3)	18·8 (4·5)	20·2 (4·7)	22·5 (4·4)
Sleep disturbance	24·4 (5·1)	24·0 (5·2)	25·4 (4·6)	25·7 (4·8)	26·0 (4.9)	24·3 (4·2)	24·3 (4·4)	25·9 (4·5)	26·8 (4·7)	27·2 (4·4)
Constipation	22·3 (3·8)	21·8 (3·9)	21·6 (4·4)	22·0 (4·3)	22·8 (4·2)	23·4 (4·1)	23·3 (4·3)	24·7 (3·8)	25·8 (3·9)	25·6 (4·0)
Diarrhoea	20·7 (3·6)	21·1 (3·5)	21·6 (3·4)	22·5 (3·2)	22·4 (3·6)	21·0 (3·7)	21·6 (3·3)	22·3 (3·5)	22·0 (4·0)	23·3 (3·8)

Data are mean (SD).

Table 3: **EORTC QLQ-C30 scores**

although prophylactic surgery is generally used for patients with advanced gynaecomastia.[12]

Findings from studies[8] on patients with prostate cancer who were given the oestrogen antagonist tamoxifen confirm that hormonal treatment can restore a healthy balance of oestrogen and androgen.[13,14] Boccardo and colleagues[13] and Saltzstein and co-workers[14] assessed the role of tamoxifen versus anastrozole in the prevention of gynaecomastia and breast pain induced by bicalutamide monotherapy. Both studies showed that tamoxifen was effective and that anastrozole did not significantly reduce the frequency of gynaecomastia and breast pain.

The most commonly used treatment for patients with gynaecomastia is low-dose irradiation, especially as prophylaxis. Studies[9] of prophylactic breast irradiation, before oestrogen or antiandrogen therapy, have reported effectiveness for this approach in many patients. Tyrrell and colleagues[15] have shown that prophylactic breast irradiation is an effective and well tolerated strategy for prevention of bicalutamide-induced gynaecomastia: a 10-Gy dose of electron-beam radiotherapy significantly lowered the frequency of gynaecomastia induced by bicalutamide from 45 to 28 of 53 patients (p=0·0008). Van Poppel and co-workers[16] assessed the effectiveness of localised radiotherapy (two fractions each of 6 Gy, given as external-beam radiotherapy) in 51 patients receiving 150 mg bicalutamide for treatment of non-metastatic prostate cancer. Use of radiotherapy reduced the severity of bicalutamide-induced gynaecomastia, breast pain, or both in about a third of patients.

The frequency of gynaecomastia in our study (69%) was similar to that reported in the EPC programme (68%) and in that of Boccardo and colleagues[13] (73%). Furthermore, our findings are in agreement with previous reports of different treatment schedules, such as those used by Boccardo and collagues[13] and Saltzstein and co-workers[14] (who both used 20 mg tamoxifen per day) and those by Eaton and colleagues,[17] who used 20 mg tamoxifen per week. Because there is no consensus on the optimum schedule, we decided to use the lowest available daily dose of the drug (ie, 10 mg).

There are some concerns about the use of tamoxifen in prostate cancer. Although blocking the effects of oestrogen might effectively prevent or treat gynaecomastia, the consequences of such treatment are unknown. Tamoxifen could increase androgen secretion by blocking the negative feedback of oestradiol on the hypothalamic-pituitary axis. Therefore, clinical trials addressing this issue are needed. However, PSA response rates were not affected by tamoxifen treatment in our trial or in other previous studies.[13,14,17]

The frequency of gynaecomastia after radiotherapy in our trial was 34%—lower than that reported by Tyrrell and colleagues[15] (52%) and similar to that reported by Widmark and co-workers[18] (28%). Differences between studies may have been a result of different doses of radiation. However, it was not possible for us to compare different radiation doses or schedules, and to our knowledge no such studies have been done.

The frequency of gynaecomastia for patients assigned bicalutamide alone and subsequently allocated to radiotherapy were more favourable (ie, 44%) than for findings in a similar group reported by Van Poppel and co-workers,[16] who showed a reduction in gynaecomastia in a third of patients assigned to bicalutamide alone compared with radiotherapy. This difference might have resulted from different regimens (12 Gy in one fraction *vs* two fractions of 6 Gy, respectively). Moreover, application of a bioequivalence equation shows that one dose of 12 Gy potentially exposes breast tissue to higher doses of radiation than 12 Gy given in 2–3 fractions.[19]

The adverse events of bicalutamide alone and in combination with tamoxifen or radiotherapy were much the same as those recorded in previous studies.[12,13] Furthermore, groups did not differ in quality of life. Radiotherapy-associated adverse events were similar to those seen in previous studies[15,16,18]—ie, all effects were transient and resolved spontaneously. Our aim was to keep to a minimum the risk of adverse events and

inconvenience for the patient by giving one low dose of radiation. Although increasing the dose or field size might reduce the frequency of gynaecomastia, it could also increase the risk of adverse events associated with radiotherapy. Therefore, comparisons of different radiation schedules are awaited. Late cardiopulmonary effects and secondary malignant disease are further concerns when irradiating the breast.[20] However, we are not aware of any reports of secondary malignant disease associated with single doses of radiation at 10–12 Gy.[21] We found that groups did not differ in PSA relapse. Therefore, the findings from the EPC programme on the efficacy of bicalutamide monotherapy for prostate cancer were confirmed in our study.

We are aware that our study has several limitations. First, for this unsponsored, spontaneous trial to be designed as a blinded study, a third institution responsible for treatment assignment would have been needed, and this proved difficult to organise. Second, the use of placebo controls was another point of discussion in the preparation of the protocol, but evidence at that time that some treatment (ie, radiotherapy or medical or surgical therapy) could effectively reduce gynaecomastia or breast pain induced by bicalutamide[8] meant that we considered it more ethical to offer actual treatment to patients. Third, pain was not patient-reported—ie, it was arbitrarily scored according to severity as none, mild, moderate, or severe after direct patient questioning, and thus a Visual Analogue Scale (VAS) or specific questionnaire was not used. However, assessment of breast pain was done on the basis of the patients' feelings and sensations, even if mediated by the investigators. The same assessment method has been used in other trials,[13,15] and is more practical to use, even if less reproducible.

In conclusion, we have shown that tamoxifen and radiotherapy prevented gynaecomastia and breast pain in some patients receiving bicalutamide monotherapy for prostate cancer, and that tamoxifen was more effective than was radiotherapy in prevention and treatment of such gynaecomastia and breast pain. Because assessment of survival needs more patients and longer follow-up than that of our study, we could not assess survival as a primary endpoint. Future comparisons of tamoxifen plus bicalutamide with bicalutamide alone, with survival as the primary endpoint, would be of interest.

Contributors

S Perdonà wrote the protocol and was responsible for randomisation. R Autorino selected the patients after primary surgery, analysed the data, and contributed to the writing of the article. S De Placido designed the study, statistical methods, and follow-up of patients. M D'Armiento selected patients after primary surgery. A Gallo selected patients after primary radiotherapy and was responsible for randomisation. R Damiano assessed patients. D Pingitore was the radiotherapist. L Gallo assessed patients after primary surgery and radiotherapy and was responsible for randomisation. Prof M De Sio and Prof A R Bianco were responsible for follow-up of patients. G Di Lorenzo coordinated the study, analysed the data, and contributed to the writing of the article.

Conflict of interest

We declare no conflicts of interest.

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