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The Effect of Danazol on Tumour Control and Weight Loss in Patients on Tamoxifen Therapy for Advanced Breast Cancer: a Randomised Double-blind Placebo Controlled Trial

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To assess the effect of danazol in advanced breast cancer 183 patients were randomised to receive either tamoxifen plus danaxol or tamoxifen plus placebo. Patients underwent systemic work-up pretreatment then every 12 weeks or sooner if they clinically progressed. There were no differences in objective response rates with tamoxifen plus danazol vs. tamoxifen plus placebo (27% vs. 24%), time to progression (median 6.4 vs. 6.2 months) or survival (median 22.6 vs. 23.5 months) when the two arms were compared (all $P > 0.5$). The addition of danazol to tamoxifen had no effect on time to progression when adjusted for significant prognostic factors in a multivariate analysis. However, it was found incidentally that weight was stable on tamoxifen plus danazol (average gain 0.6 kg, S.E. 0.6 kg) compared with a significant loss on tamoxifen plus placebo (average loss 2.0 kg, S.E. 0.6 kg, $P = 0.003$). The average weight was maintained on tamoxifen plus danazol even in patients who did not respond to treatment.
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INTRODUCTION

TAMOXIFEN is an anti-oestrogen which blocks the uptake of oestrogen in breast tissue by binding to the oestrogen receptor. Tamoxifen has been used extensively in patients with breast cancer. In oestrogen receptor positive patients with advanced disease, reponse rates of approximately 50% have been reported, compared with 20–50% for oestrogen receptor unknown patients and less than 10% for oestrogen receptor negative patients [1–5]. While this treatment has provided successful palliation of symptoms in advanced disease, it is important to explore ways in which tamoxifen therapy can be improved.

Danazol (17α-pregna-2,4-dien-20-yno(2,3-D)isoxazol-17β-ol) is a synthetic steroid and a mild androgen, without oestrogenic or progestational activity, which blocks the release of pituitary gonadotrophins [6]. Danazol has been used for many years in endometriosis, precocious puberty, benign breast disease and hereditary angioneurotic oedema. Side-effects are usually mild and dose-related [7, 8]. Danazol causes regression of established breast tumours in 9,10-dimethyl-1,2-benzanthracene treated rats [9]. Phase II trials suggest that danazol produces responses in approximately 17% of patients with advanced breast cancer [10]. Powles *et al.* reported that patients with advanced disease treated with tamoxifen, danazol and aminoglutethimide achieved a significantly higher response rate than with tamoxifen alone [11].

In addition, a known side-effect of danazol is weight gain. Other hormones such as megestrol acetate have been shown to stabilise weight loss or produce weight gain in cachectic cancer patients [12]. Thus, a further possible benefit from the addition of danazol could be control of weight loss in advanced breast cancer.

The combination of tamoxifen plus danazol was compared to tamoxifen plus placebo in this phase III randomised double-blind trial.

PATIENTS AND METHODS

Patients

Patients eligible for this study were those with histologically proven stage III or IV breast cancer using the American Joint Committee staging criteria [13]. Patients had measurable or evaluable disease, postmenopausal status and had not previously received tamoxifen or danazol. Patients with rapidly progressive or extensive visceral disease were ineligible.

Study design

Eligible patients were randomised to receive either tamoxifen plus danazol or tamoxifen plus placebo. The placebo resembled danazol in size, colour, shape and taste. The study was double-blinded with both patients and treating physicians unaware of which study drug was given. The method of randomisation was based on a randomised block design.

Treatment plan

Patients on both arms received tamoxifen 20 mg orally daily. In addition, patients received either danazol 200 mg or a placebo orally daily. All treatment was given until there was clear evidence of disease progression.

Study parameters

Known disease was documented at trial entry by clinical examination, serum biochemistry, bone scan or skeletal survey if the bone scan was positive, liver scan, chest X-ray and full

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blood examination or computer tomography (CT) scans as required. Clinical examinations, measurements of weight, full blood examination and serum biochemistry were planned to be repeated 4-weekly. Scans and X-rays required to follow the disease were repeated every 12 weeks or earlier if there was clinical suspicion of progression. Standard WHO response criteria were used [14]. Toxicity was assessed clinically every 4 weeks while on study drugs.

Statistical methods

Overall survival, time to progression (all patients) and time to relapse (responders only) were estimated using the Kaplan–Meier product-limit method, and the Mantel–Cox log-rank test was used to test comparisons between groups. Confidence intervals (CI) for median survival times were calculated using the Brookmeyer–Crowley method.

Overall survival was calculated from the date of randomisation to the date of death from any cause or the closing date (28 Feb 1989) for patients who were still alive.

Time to progression was calculated from the date of randomisation to the date of progression with censoring at the closing date. If a patient died prior to the closing date without a date of progression being recorded, the date of death was taken as the date of progression, unless the patient died of an unrelated cause. Time to relapse was calculated from the date of achieving best response for all patients who achieved a complete or partial response.

Response rates for the two arms and various prognostic factors were compared using the Yates corrected χ^2 test or the χ^2 test for trend. Weights of patients on the two arms were compared using the t-test with pooled variance.

With the exception of oestrogen and progesterone receptors, all prognostic factors found to have a significant influence on time to progression in univariate analyses were tested jointly in a multivariate analysis using the Cox proportional hazards model. ECOG performance status and the number of metastatic sites were included as continuous variables and the other factors were included as indicator variables. Only patients with all variables known were included. Receptor status was omitted because it was unknown for a large proportion of patients. Treatment arm was then included in the model with all variables which were significant at a level of $P = 0.05$.

BMDP statistical software was used for the analysis [15].

Ethical considerations

The protocol complied with the National Health and Medical Research Council of Australia's guidelines on human experimentation and the protocol was reviewed and approved by the Peter MacCallum Cancer Institute's Ethics Committee. All patients gave written informed consent prior to randomisation.

RESULTS

184 patients were randomised, although 1 patient was subsequently excluded because she was not postmenopausal and hence did not satisfy the eligibility criteria. Of the 183 patients analysed, 92 were treated with tamoxifen plus danazol and 91 with tamoxifen plus placebo (Table 1). The two arms were well balanced for on-study characteristics. Over 75% of patients were ECOG performance status 0 or 1 and 54% of patients had bone, skin or lymph node disease without visceral involvement. 93% of the patients on the tamoxifen plus danazol arm and 98% on the tamoxifen plus placebo arm had stage IV disease.

8 patients on the tamoxifen plus danazol arm and 14 patients on the tamoxifen plus placebo arm were non-evaluable for response. 4 patients had equivocal metastatic disease, 4 patients without progression received radiotherapy or surgery to marker lesions, 11 patients died of disease or other causes before the first assessment (4 on danazol, 7 on placebo) and 3 patients were lost to follow-up. All 183 randomised patients are included in the analyses of time to progression and survival.

Table 1. On study patients' characteristics

	Tamoxifen + danazol	Tamoxifen + placebo
Number randomised	92	91
Median age at randomisation (years)	63	62
Median time from initial diagnosis to recurrence or advanced disease (months)	23	22
Stage		
III	7%	2%
IV	93%	98%
Oestrogen receptor		
Positive (>10 fmol/mg protein)	50%	59%
Negative (≤10 fmol/mg protein)	14%	9%
Unknown	36%	32%
Progesterone receptor		
Positive (>10 fmol/mg protein)	30%	45%
Negative (≤10 fmol/mg protein)	25%	18%
Unknown	45%	37%
Prior endocrine therapy		
Oophorectomy	11%	9%
Stilboestrol	1%	0%
None	88%	91%
ECOG performance status*		
0	64%	64%
1	11%	21%
2	13%	10%
3	9%	4%
Unknown	3%	1%
Initial sites of disease		
Bone	57%	60%
Skin	30%	26%
Lymph nodes	22%	29%
Lung	18%	24%
Pleura	14%	23%
Breast	17%	13%
Liver	9%	10%
Other	9%	12%

*ECOG = Eastern Cooperative Oncology Group.

There were no significant differences in response rates when the two arms were compared. On the tamoxifen plus danazol arm, 27% of all patients achieved an objective response (95% CI: 18–37%), 9% with complete response (CR) and 18% with a partial response (PR), and 27% of patients remained stable (SD). On the tamoxifen plus placebo arm, 24% achieved an objective response (95% CI: 16–34%) including 2% CR and 22% PR, and 25% had SD. CR occurred at all the major sites except bone and liver. There were no significant differences between the arms in objective response rates at the various major sites.

The median time to disease progression for the tamoxifen plus danazol arm was 6.4 months (95% CI:4.7–11.4 months) and 6.2 months (95% CI:4.3–8.2 months) for the tamoxifen plus placebo arm with no significant difference between the two arms ($P = 0.58$). For patients who achieved CR or PR there was no significant difference between the treatment arms in time to relapse ($P = 0.94$).

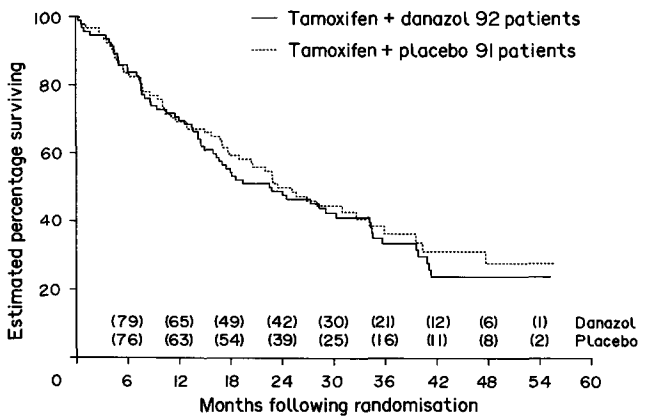

Fig. 1. Overall survival comparison of tamoxifen plus danazol vs. tamoxifen plus placebo (P = 0.62). Numbers in brackets refer to the number of patients at risk at the beginning of each 6 month period.

There was no significant difference in survival between the two arms with a median survival of 22.6 months for tamoxifen plus danazol (95% CI:16.0–30.3 months) and 23.5 months for tamoxifen plus placebo (95% CI:17.9–32.7 months, P = 0.62) (Fig. 1). No significant difference in survival was detected between the two arms when 5 patients who died of causes other than breast cancer were censored at their time of death (P = 0.53).

55% of patients on tamoxifen plus danazol and 63% of patients on tamoxifen plus placebo had no side-effects (P = 0.4). There were no significant differences between arms when comparing each toxicity which occurred in at least 5 patients (Table 2). Acne and hot flushes each occurred in 4 patients. The major toxicity encountered was nausea and vomiting in 23% of patients with no significant difference between the arms. When patients were grouped according to their most severe toxicity grade, there was no significant difference between the arms (P = 0.16, χ^2 test for trend).

Unfortunately, only 50% of patients were weighed prior to commencing treatment. 71% of these were weighed subsequently while on treatment. There was no significant difference between the treatment arms in the pretreatment distribution of weight in patients on the study (P = 0.88). Weight was stable in patients on the tamoxifen plus danazol arm (average gain 0.6 kg, S.E. 0.6 kg, 33 patients) compared with significant weight loss on the tamoxifen plus placebo arm (average loss 2.0 kg, S.E. 0.6 kg, 32 patients, P = 0.003).

Table 2. Toxicity of treatment

Toxic effect	Arm	None (%)	Mild (%)	Moderate (%)	Severe or intolerable (%)
Nausea or vomiting	Danazol	74	15	9	2
	Placebo	79	12	7	2
Vaginal discharge	Danazol	91	4	4	0
	Placebo	93	7	0	0
Indigestion/anorexia	Danazol	96	3	1	0
	Placebo	97	2	1	0
Oedema	Danazol	98	1	1	0
	Placebo	97	2	1	0
Hirsutism	Danazol	97	2	1	0
	Placebo	98	2	0	0

16 of 33 patients on tamoxifen plus danazol gained from 1 to 7 kg compared with only 4 of 32 patients on tamoxifen plus placebo. For each category of response the average weight was maintained on the tamoxifen plus danazol arm even in patients with stable or progressive disease. In contrast, only the CR group on the tamoxifen plus placebo arm gained weight. The average weight was reduced by 1 to 12 kg for 22 of 32 patients on tamoxifen plus placebo compared with 12 of 33 on tamoxifen plus danazol. The significant difference in weight change between the treatment arms remained when adjusted for response category in an analysis of variance. It must be noted that control of weight loss was not one of the main aims of the study and data were available for only 36% of the patients.

General sense of well being or appetite or other quality of life parameters were not recorded in this study. However, ECOG performance status was noted throughout. There was no significant change in performance status in either arm while on study drugs.

Univariate analysis of prognostic factors revealed that the time between initial diagnosis and advanced or recurrent disease, number of metastatic sites, visceral involvement, oestrogen receptor level, ECOG performance status, age and chemotherapy prior to study entry all had a highly significant influence on time to progession and survival (Table 3). Progesterone receptor level had a significant influence on time to progression only. Patients with more than 2 years between the diagnosis of advanced disease and randomisation had significantly longer time to progression than patients entered on the trial earlier but the difference in survival was not significant (Table 3).

Oestrogen receptor levels of 0–10 fmol/mg protein were associated with 14% objective response, 11–100 fmol/mg protein with 29% and >100 fmol/mg protein with 38% (P = 0.061, trend). Progesterone receptors of 0–10 fmol/mg protein were associated with 21% objective response, 11–100 fmol/mg protein with 30% and >100 fmol/mg protein with 48% (P = 0.027, trend). Patients with ECOG performance status grade 0 had 31% objective response, grade 1 17%, grade 2 14% and grade 3 17% (P = 0.055, trend). Patients with prior chemotherapy had 15% objective response while those without had 30% (P = 0.038). Multivariate analysis of time to progression on the subset of 176 patients with known values for all variables, except receptors, revealed that shorter time to progression was significantly associated with higher grade performance status, age younger than 55, less than 12 months between initial diagnosis and advanced disease, and increased number of metastatic sites. Longer time to progression was associated with more than 2 years between developing advanced disease and randomisation on this trial (Table 4). The addition of danazol to tamoxifen had no significant effect on time to progression when the above five significant prognostic factors were included in the model (P = 0.84).

DISCUSSION

Endocrine combinations in advanced breast cancer have produced equivocal results compared with single agent endocrine therapy [5]. Prednisolone when added to either oophorectomy or tamoxifen has improved response rates [16]. A randomised trial of the combination tamoxifen, aminoglutethimide and danazol produced improved response rates over tamoxifen alone, but no difference in time to progression or survival [11]. Randomised trials of tamoxifen plus aminoglutethimide have produced equivalent results to tamoxifen alone [17, 18]. Danazol is a mild androgen which blocks release of pituitary gonadotrophins with modest activity as a single agent in advanced breast

Table 3. Univariate analyses of prognostic factors

Factor	No. of patients	Time to progression median (months)	P*	Survival median (months)	P*
Months from initial diagnosis to advanced disease					
0–12	64	4.0		14.6	
13–60	75	6.9		22.8	
>60	40	12.6	0.0001	41.4	<0.0001
Unknown	4				
Number of metastatic sites					
0	11	26.9		Not reached	
1	78	7.1		30.3	
2	48	6.1		22.6	
3	28	4.3		15.1	
4 or 5	18	3.1	0.0006	12.0	<0.0001
Visceral involvement					
No	99	11.4		34.2	
Yes	84	4.0	0.008	15.1	0.0005
Oestrogen receptor (fmol/mg protein)					
0–10	21	3.4		13.6	
11–100	56	6.4		25.2	
>100	40	10.7	0.015	34.2	0.002
Unknown	66				
Progesterone receptor (fmol/mg protein)					
0–10	39	4.6		19.0	
11–100	44	6.9		22.6	
>100	23	10.7	0.021	35.7	0.14
Unknown	77				
ECOG performance status					
0	117	10.6		34.2	
1	29	4.0		22.6	
2	21	3.7		8.7	
3	12	1.4		6.1	
Unknown	4		<0.0001		<0.0001
Age at randomisation (years)					
≤54	45	3.3		17.1	
≥55	138	8.4	0.002	29.1	0.005
Prior chemotherapy					
No	128	10.6		34.2	
Yes	55	3.1	<0.0001	13.0	<0.0001
Months from advanced disease to randomisation					
0–24	165	6.0		22.8	
>24	14	16.1	0.012	34.4	0.095
Unknown	4				

*P value from log rank test for difference between two subgroups or trend across three or more subgroups.

cancer. Thus it was a possible candidate for an endocrine combination with an agent with a different mechanism of action. In this randomised double-blind placebo controlled trial, danazol added to tamoxifen did not improve tumour control measured by a comparison of response rates, remission duration, time to progression or survival.

Table 4. Multivariate analysis of factors influencing time to progression (based on 176 patients)

Factor	Estimated relative hazard*	95% CI	P
Performance status at randomisation	1.5	1.3–1.8	<0.0001
Age at randomisation ≤54 years	2.0	1.4–3.0	0.0003
0–12 months between initial diagnosis and advanced disease	1.7	1.2–2.5	0.002
Number of metastatic sites	1.2	1.0–1.4	0.033
>24 months between advanced disease and randomisation	0.4	0.2–0.8	0.005
Tamoxifen plus danazol	1.0	0.7–1.3	0.84

*Estimated relative hazards and P values for model containing all six variables.

It was initially planned to accrue 200 patients but the study was stopped at 183 patients because of slow accrual towards the end of the trial. It was apparent from an analysis at this stage that it was most unlikely that an additional 17 patients would substantially affect the conclusions of the study.

Patients on tamoxifen plus danazol were able to maintain their weight even with a substantial volume of disease while stable or progressing. This experience was significantly different for patients on tamoxifen plus placebo who experienced a mean weight loss of 2 kg while on study drugs. Only 31% of monitored patients gained weight while on study. Similar observations have been made with progestational agents [12, 19–21]. In two randomised placebo controlled trials, megestrol acetate significantly improved weight in cachectic cancer patients [19, 21]. In these trials, patients on megestrol acetate reported significantly improved appetite and food intake with less nausea and vomiting. The value of this approach is now being assessed with more detailed quality of life assessments and different megestrol acetate dose schedules in a large Australian randomised double-blind trial. Our study suggests that danazol can also stabilise weight and may be a useful alternative when progestogens cannot be used. Using the current Australian pricing system, megestrol acetate at 480–800 mg per day is 6 to 10 times the price of danazol as used in this study. Thus danazol may be a cost-effective alternative for weight stabilisation.

There was surprisingly little toxicity noted in the tamoxifen plus danazol arm with the great majority of patients experiencing no or mild side-effects. At the doses used, we rarely detected unwanted virilisation with very few cases of acne or hisutism.

The response rate of 24–27% reported for this study probably closely resembles non-trial clinical practice. The median time to progression for all patients on study was 6.4 months (95% CI: 5.0–8.7 months). Time to progression was highly significantly influenced by age, performance status, time between initial diagnosis and advanced disease, number of metastatic sites and time between advanced disease and randomisation but not danazol treatment arm.

In conclusion, danazol when added to tamoxifen did not significantly improve tumour control in the 183 patients reported in this study. However, danazol significantly stabilised weight in advanced breast cancer patients treated with tamoxifen.

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Prediction of Long-term Response after High-dose Chemotherapy with Autologous Bone Marrow Transplantation in the Salvage Treatment of Non-seminomatous Germ Cell Tumours

Jean-Pierre Droz, Andrew Kramar and José-Luis Pico

High-dose chemotherapy (HDCT) and autologous bone-marrow transplantation (ABMT) are widely used in the salvage treatment of non-seminomatous germ cell tumours (NSGCT). We compiled 10 published series with NSGCT patients treated by HDCT and ABMT. Several prognostic factors for long-term non-evolutive disease (NED) were studied: dose of etoposide (ETO), oxazaphosphorine derivate (OXA) (expressed in cyclophosphamide equivalents using a cyclophosphamide/ifosfamide ratio of 1:3), platin-derivate (PLAT) (expressed in cisplatin equivalents using a cisplatin/carboplatin ratio of 1:4), disease status (refractory or responder), OXA and PLAT compounds. Strong interactions were shown between disease status and PLAT and ETO. In refractory patients, logistic regression analysis showed that the doses of OXA and PLAT increase the probability of NED. Conversely, in responder patients only ETO and OXA dosages increase the probability of NED. It is concluded that the status of the disease is the most important prognostic factor for long-term NED after HDCT + ABMT in NSGCT.
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INTRODUCTION

THE ROLE of high-dose chemotherapy (HDCT) and autologous bone marrow transplantation (ABMT) in non-seminomatous germ cell tumours (NSGCT) is currently under investigation in the settings of both salvage [1, 2] and first-line treatments [3, 4]. The major drugs used are etoposide, cyclophosphamide, ifosfamide, cisplatin and carboplatin. The response rates and long-term non-evolutive disease (NED) rates seem dramatically different in cisplatin refractory and responder patients [5, 6]. We compiled results of HDCT + ABMT as salvage treatment in NSGCT patients published either in peer reviewed journals or congress abstracts [4, 7–17]. The data were then analysed