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Danazol Treatment for Advanced Breast Cancer

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Summary. *Pre-menopausal (14) and post-menopausal (55) patients with advanced breast cancer were treated with danazol (Danol) for periods ranging between 3 days and 30 months. Of these, 10 patients (14.9%) responded to treatment for 3–19 months (mean 10 months); a further six patients (9%) showed stabilisation of disease; 45 patients showed clear progression of disease following treatment; and eight patients were unassessable. Side-effects occurred in 17 of 69 patients (25%) and necessitated a reduction in therapy in eight cases.*

It is concluded that danazol is moderately well tolerated and is an effective agent in patients with advanced breast cancer, but the response rate is inferior to that of other agents in current use, such as tamoxifen or aminoglutethimide.

Introduction

Danazol is a synthetic steroid used in the treatment of endometriosis and benign breast disease [4]. In these disorders treatment generally produces a rapid sustained relief of discomfort, and relatively few side-effects have been reported. Its mode of action is thought to be by inhibiting gonadotrophin secretion but it also has capacity to bind to the progesterone and androgen receptor [7]. It has a very low affinity for oestrogen receptor, indicating that it has a different mechanism of action from other endocrine agents commonly used in breast cancer. A previous preliminary publication detailed our experience in a small group of patients [1]. The purpose of this paper is to give results, duration of response, and survival in a larger group.

Patients and Methods

All patients treated were females with histologically proven advanced breast cancer. Their ages ranged from 34 to 84 years and all had assessable disease as defined by UICC criteria [5]. For soft tissue lesions, the sum of the products of the diameters of each lesion had to decrease by > 50% for a response to be recorded. For unidimensional lesions, response was defined as a decrease by > 50% in this dimension. Recalcification or healing of osteolytic lesions was interpreted as a response in bone. A response, as defined, had to be maintained for at least 2 months. Stabilisation of disease was defined as no change or less than a 50% reduction for a period of at least 2 months. All patients were fully staged as previously described [2] prior to, and at 2–3 months and 6–8 months after, the start of treatment. There were 14 pre-menopausal and 55 post-menopausal patients; 16 had received and responded to previous endocrine therapy but had relapsed, while 14 had failed to respond to previous endocrine therapy. No patients had received prior endocrine therapy or combination chemotherapy within 1 month of starting treatment and all patients had progressive disease.

Treatment was started at a dose of 100 mg three times daily. Two weeks later, if the patient tolerated treatment, the dose was generally increased to 200 mg three times daily. Some patients, for reasons of age or concern about fluid retention, were maintained at a dose of 300 mg a day. Treatment was continued until evidence of clear progressive disease occurred.

Oestrogen receptor was measured by the method of McGuire et al. [6]. Oestrogen receptor-positive tumours contain more than 10 fmol oestrogen receptor/mg cytosol protein.

Results

Two of the 69 patients were unassessable. One patient received dexamethasone in addition to danazol and one patient never took her tablets. Six patients stopped treatment before 3 weeks of therapy had been completed, because of either progressive disease (2 patients) or side-effects (3 patients), but these are included in the analysis.

a) Response to Therapy

Table 1 gives details of the patients, indicating their menopausal status, results of prior endocrine therapy, the oestrogen receptor status of their tumours, and the dose of tablets that they received. Responses were recorded in 10 of 67 patients (14.9%), and a further six (9%) showed stabilisation of disease. Two patients responded who had failed to respond to prior endocrine therapy with tamoxifen and aminoglutethimide, respectively. Response rates were similar whether the dose was 300 mg/day or 600 mg/day.

Mean age was similar in responders and non-responders. The 10 patients who responded included nine of 54 of the post-menopausal and one of 14 in the pre-menopausal group. Response duration was 2–19 months, with a mean response duration of 10 months.

At the present time six of 10 responders are alive, as against four of six patients whose disease showed stabilisation

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Table 1. Characteristics of patients treated

	Total	Mean age range	Menopause		No. receiving previous endocrine therapy	Previous endocrine therapy		No. of ER[a] measured	No. with ER >10 fmol/mg	Final dosage of danazol	
			Pre	Post		Response	Non-response			300 mg/d	600 mg/d
Responders	10	65 (38–84)	1	9	4	2	2	3	1	6	4
No change	6	59 (43–75)	3	3	1	1	0	1	1	2	4
Progressive disease	45	64 (34–83)	9	32	23	12	11	18	7	27	18
Unassessable	2	54	1	1	2	1	1	2	0	2	0

ER, Estrogen receptors

Table 2. Response by site

Response category	No. of patients in each category	No. of responders by site			
		Soft tissue	Lung	Liver	Bone
Responders	(10)	8	3	0	0
No change	(6)	2	0	0	6[a]
Progressive disease	(45)	27	17	2	24

[a] All patients had pain relief

and six of 45 patients who showed progressive disease. The 2-year survival rates were six of 10 (60%) for responders, four of six (66%) for stabilisers, and 10 of 45 (22%) for those with progressive disease.

Sites of disease responding to treatment are shown in Table 2, and it can be seen that patients with soft-tissue sites such as skin and lymph nodes appear to respond favourably to treatment. The majority of patients with bone metastases were not helped by treatment but three patients whose disease showed stabilisation experienced significance pain relief.

b) Dosage and Side-Effects

Three patients could not take danazol as they suffered severe vomiting and headaches within a week of starting therapy. The remaining patients were able to take the tablets but a total of 17 patients suffered side-effects. The commonest side-effect was amenorrhoea in pre-menopausal patients (5 patients), but nausea and vomiting (4 patients), weight gain (2 patients), and oedema (3 patients) were occasionally seen. Alopecia, hirsutism, and hot flushes were also troublesome in a few patients. Treatment was well tolerated in the majority of patients.

c) Treatment in Pre-Menopausal Patients

Only one of 14 pre-menopausal patients showed clear evidence of response, and this patient subsequently responded to oophorectomy when the disease relapsed. However, a further three pre-menopausal patients showed stabilisation of disease for 29, 9, and 7 months, respectively and in two of these patients disease subsequently stabilised after oophorectomy. One patient had a withdrawal response on stopping danazol and subsequently responded to oophorectomy. All three of these pre-menopausal patients are alive and all have been followed-up for at least 2 years.

Discussion

This publication confirms our previous report [1] in which we described our initial experience with this drug. It appears to have an effect in both pre- and post-menopausal patients with advanced breast cancer. However, patients appear to respond less frequently than with aminoglutethimide or tamoxifen [8]. Side-effects were seen in a significant percentage of patients and certainly were more frequent than we observed in patients receiving tamoxifen. It seems that this form of treatment may be a suitable 'second-' or 'third-line' therapy after a response has been seen with one of the standard agents. Its use as a 'first-line' treatment seems to be unjustified, since the response rate seems inferior to those seen in patients treated with more conventional agents.

We have studied the effects of danazol on hormones, and the results indicate that significant depression of gonadotrophin occurs in post-menopausal patients, though no other consistent changes in steroid hormones were seen [3]. The addition of tamoxifen and aminoglutethimide to danazol does not produce any further suppression of gonadotrophins [3].

In view of the significant activity of this compound, we have evaluated its use in combination with tamoxifen and aminoglutethimide. Preliminary results indicate, however, that survival is not prolonged by the combination, although response rates is improved [8].

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