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Primary Chemotherapy with Mitoxantrone and Prednisone in Advanced Breast Carcinoma. A Phase II Study

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Abstract—*Thirty-seven evaluable patients with progressive disseminated breast carcinoma were treated with a combination of mitoxantrone* 14 mg/m^2 *i.v. every* 3 *weeks plus prednisone* 20 mg/m^2 *p.o. daily with a reducing dose over several weeks. Thirteen of* 37 *patients* (35%) *achieved an objective response with two complete regressions. The median duration of response was* 7 *months and the median duration of survival* 14 *months.The cardiac function of all patients was monitored by serial left ventricular ejection fraction, at rest and after stress, and* 3*-monthly thereafter. Ten patients showed a deterioration in the ejection fraction after a minimum cumulative dose of* 86 mg/m^2 *(six cycles), but only four developed clinical cardiac failure which was easily reversible after stopping mitoxantrone. Leucopenia was the dose-limiting toxicity. Nausea and/or vomiting were generally mild and transient. Alopecia was minimal. These results confirmed that this combination is effective and well tolerated in the treatment of disseminated breast carcinoma, and cardiotoxicity can be avoided with adequate monitoring of the left ventricular ejection fraction after six cycles of therapy* (86 mg/m^2).

INTRODUCTION

IN THE last few years, new drugs and different combinations have been tested in the cytotoxic chemotherapy of disseminated breast carcinoma to increase the effectiveness and minimize the side-effects caused by the agents currently in use. Because of the failure to cure patients with disseminated forms of the disease, the treatment of advanced breast cancer is palliative in intent. This encourages us to continue to test new cytotoxic effective agents.

Recently, mitoxantrone, a semi-synthetic amino-anthraquinone, was introduced and claimed to have considerable antitumoral activity in patients with metastatic breast carcinoma in several phase II studies [1–6]. It was also observed to be free from alopecia, gastro-intestinal side-effects or cardiotoxicity. To study further the effectiveness and toxicity of this new compound, we have carried out a phase II study of mitoxantrone and prednisone, as primary cytotoxic chemotherapy for disseminated breast carcinoma. The inclusion in this schedule of prednisone was intended to increase the well-being of the patients and to stimulate the bone marrow to minimize the myelosuppressive effect of mitoxantrone, its dose-limiting toxicity [7].

PATIENTS AND METHODS

Thirty-eight women with locally advanced or disseminated breast carcinoma, histologically proven, previously untreated with cytotoxic chemotherapy but resistant to endocrine treatment or who were estrogen receptor negative, were included from 1 April 1984 until 30 June 1986 (last follow-up 31 February 87) in this study. Twenty-eight patients had received prior standard radiotherapy at the primary site or as an adjuvant to surgery, but in all of the cases there had been a complete recovery from the bone marrow suppression. All the patients in the trial showed progression of the disease and hormonal treatment had been discontinued for at least 4 weeks before they entered into this study. Eligibility criteria included the presence of evaluable disease, no previous chemotherapy (adjuvant or for advanced disease), age ≦65 years, a performance status ≧20% (Karnofsky scale), adequate hepatic and renal function tests, a white blood count ≧4000 cells/μl, a platelet count ≧100,000/μl. Patients with symptoms or signs of brain metastases,

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osteoblastic bone lesions and pleural effusions as the sole manifestations of disseminated disease were excluded from the protocol. Cardiac function had to be found normal by clinical examination, electrocardiogram (ECG) and a base line radioisotopic gated angiography for measurement of left ventricular ejection fraction (LVEF) both at rest and in response to stress. Cardiac assessment was repeated after every four courses of treatment [8, 9].

The schedule of chemotherapy consisted of mitoxantrone 14 mg/m^2 i.v. over 30 min, every 3 weeks, plus prednisone 20 mg/m^2 p.o. daily for 3 weeks, with subsequent progressive reduction of the dose, but maintaining a daily dose for 4 weeks more and then continuing with 10 mg/m^2 on alternate days. Cytotoxic chemotherapy was planned for a total of eight cycles. Patients who were still responding after eight courses continued with the same treatment until evidence of cardiotoxicity or objective progression of the disease. The criteria adopted for evaluation of cardiotoxicity were based on signs or symptoms of left ventricular failure, and/or a deterioration in LVEF 15% or greater of base line values. The following dose modifications were adopted in presence of myelosuppression. With a white blood count between 2000 and 3999 cells/μl and a platelet count between 90,000 and 99,999, the dose of mitoxantrone was delayed for 1 week only when recovery of the leucocyte count to ≧4000/μl and a platelet count to ≧100,000/μl allowed full dosage to be given. With a white blood count below 2000 cells/μl and a platelet count ≦90,000, the chemotherapy was stopped until the level of leucocytes reached ≧4000 and platelets ≧100,000. This delay was never more than 2 weeks.

Before each course of therapy a full physical examination was performed, including a full blood count and platelets. All palpable or superficial lesions were measured in two perpendicular diameters and visible lesions photographed. Skeletal and visceral disease was evaluated by adequate scans, radiographs and ultrasonograms every 3 months. Cardiac function was reassessed using repeated ECG and the determination of LVEF every 3 months.

The courses of cytotoxic chemotherapy were usually given on an out-patient basis and at least two cycles of therapy were administered before the regimen was considered ineffective. Treatment was evaluated for overall response rate, the median duration of response, the median time and toxicity. Assessment of response was performed according to the criteria recommended by the UICC [10].

Complete response (CR): total disappearance of all evidence of tumor.

Partial response (PR): a 50% or more decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions, without appearance of new ones.

Stable disease (SD): lesions unchanged (less than 50% decrease or less than 25% increase in the size of measurable lesions).

Progressive disease (PD): an increase 25% or more in the size of measurable lesions and/or appearance of new ones. When some regress while others progress or new lesions appear (mixed response) this is considered progressive disease.

The response to treatment was evaluated by at least two sequential observations not less than 4 weeks apart. All the patients with stationary status were included in the non-responders group.

The duration of response was measured from the date of initiation of cytotoxic chemotherapy to any evidence of progression. Survival was calculated from the first cycle of therapy or date of the last follow-up (31 March 1987) for the patients still alive, and was analyzed by the life-table method. Toxicity assessment was performed according to the World Health Organization (WHO) criteria [11].

RESULTS

The clinical characteristics of the patients are shown in Table 1. Thirty-seven out of 38 patients entered into this trial were eligible for assessment of response and toxicity. One patient was lost for follow up having received only one cycle of therapy. Patients were considered evaluable if they received at least two courses of chemotherapy. Patients in progression were withdrawn from this protocol and treated with a modified CMFP regimen, used in our clinic [12] or by other experimental cytotoxic drugs.

Antitumor effects

The results of this study are shown in Table 2. The overall response rate was 35% (13/37) with two complete responses and a further two patients with stable disease for 5 and 7 months. Responses were seen at all disease sites, breast, skin, lymph nodes, bone, pleural/lung and liver (Table 3). The median duration of response was 7 months (range 4–17) and the median duration of survial 14 months (range 3–27+)—last follow up: 31 March 1987. From the 37 patients selected for this trial, 15 are still alive, two in complete remission and six with partial response. Sixteen patients did not receive second-line chemotherapy. In the other 16 patients, who did not respond to mitoxantrone, three responded subsequently to a CMFP regimen. Five responders to mitoxantrone responded to a second-line chemotherapy. In 24 patients previously treated with additive and/or ablative hormotherapy there were 10 objective responses to mitoxantrone only three of these patients were without prior endocrine therapy.

Table 1. Characteristics of patients

Number of patients	37
Median age at diagnosis (years)	53.5 (range 32–64)
Median time from diagnosis to chemotherapy (months)	29.5 (range 1–128)
Previous treatments	
Mastectomy ± radiotherapy	25
Axillary involvement	
N+	15
N−	10
Primary radiotherapy ± mastectomy	12
Oophorectomy	12
Androgens and/or antiestrogens	24
Post-operative disease-free interval	
None	2
<2 years	13
≧2 years	10
Menopausal status	
0–1 years	15
1–5 years	7
>5 years	15
Sites of tumor involved	
Soft tissue	
Breast	7
Skin	10
Lymph nodes	10
Osseous	15
Visceral	
Pleura/lung	12
Liver	3
Estrogen receptors status	
ER positive	9
ER negative	10
ER unknown	18
Median performance status (range %)	50 (20–90)

Table 2. Objective responses

	Number of patients (37)	
Objective regressions		
Complete response	2 (5%)	13 (35%)
Partial response	11 (30%)	
Duration of response		
Median (months)	7	
Range	4–17	
Median survival (months)	14	
Range	3–27+	

Table 3. Response with regard to sites involved

Sites	Response	Number involved
Breast	1	8
Skin	4	9
Lymph nodes	8	10
Bone	3	15
Pleura/lung	5	12
Liver	1	3

Table 4. Toxicity

	Number of patients (37)
Hematologic toxicity	
Leucocyte nadir (per μl)*	
≧4000	14
3999–3000	7
2999–2000	12
1999–1000	4
<1000	—
Platelet nadir (per μl)*	
≦100,000	—
Nausea and/or vomiting†	20
Alopecia	
Mild	5
Severe and/or total	1
Cardiotoxicity (clinical)	4
Sepsis	—

*At day 21 of cycle.
†WHO grade 2 or 3.

Toxicity

Toxicity is shown in Table 4 and consisted mainly of a depression in the leucocyte count, the nadir being reached on the 14th day after administration of the drug, in all cases reversible. Leucopenia, grade 2–3, never 4, based on nadir at day 21 of the cycle, was observed in 13 patients (38%). Nausea and/or vomiting (grade 2–3, well controlled with metoclopramide), were registered in 20 patients, and alopecia in six, but only one required a wig. The majority of treatment courses were administered at 3-week intervals, as initially planned, and without adjustment of doses. Only one patient was withdrawn from the protocol because of prolonged leucopenia after three cycles of mitoxantrone. The number of courses given ranged from two to 15 (median 6), with a median cumulative dose of 86 mg/m^2 (range 25–210 mg/m^2).

Serial determinations of LVEF were recorded in all the patients, at rest and after stress, at 3-monthly intervals. Ten out of 37 patients showed a deterioration equal to or greater than 15% in the ejection fraction after a minimum cumulative dose of 86 mg/m^2 (six cycles), but only four developed clinical cardiac failure, which was easily reversible after stopping mitoxantrone with normalization of the ejection fraction. In these 10 patients, the median dose of mitoxantrone administered was 98 mg/m^2 with a range of 86–130 mg/m^2. No cases of sepsis or drug-related deaths occurred.

DISCUSSION

This study confirms a substantial activity of mitoxantrone against disseminated breast carcinoma with a response rate of 35%. The percentage of objective regressions obtained with this combination of mitoxantrone plus prednisone is similar to that reported by other investigators [1–6]. The regimen used here was well tolerated and the majority of patients experienced only mild and transient gastrointestinal intolerance and no alopecia. Severe or irreversible cardiotoxicity was not observed in this trial, probably because all the patients were monitored by gated angiocardiography in addition to repeated clinical cardiac examination and electrocardiogram. Also, there was a strict selection of patients on the basis of age, always less than 65 years old, and this could be another reason to diminish a potential severe cardiotoxicity. Based on the results obtained, we can conclude that mitoxantrone can be administered safely to a total cumulative dose of 86 mg/m$_2$. After this dose, regular monitoring of the LVEF is necessary. With these precautions, it is possible to stop the administration of mitoxantrone before severe or irreversible myocardial damage occurs.

Furthermore, the primary use of this schedule of chemotherapy does not seem to compromise the efficacy of CMFP used subsequently.

To attempt to increase the response rate and retain the low toxicity of cytotoxic chemotherapy used in the treatment of breast carcinoma, a new study has been initiated, in which mitoxantrone, mitomycin C and prednisone are combined as first line therapy for this disease.

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