First-line combination chemotherapy with mitoxantrone and cyclophosphamide in advanced breast cancer

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Summary

In this study, 30 evaluable patients with advanced carcinoma of the breast were treated with cyclophosphamide 600 mg/m² i.v. followed one day later with mitoxantrone (Novantronc® dihydroxyanthracene-dione) 16 mg/m² i.v. Drug treatment was repeated every 3–4 weeks, for a maximum of 12 cycles. The overall response rate was 43%; five of 30 patients (16%) attained a complete remission, and eight of 30 (27%) had a partial remission. Median response duration was 12+ months. The greater number of responses was seen in skin and soft tissues. Hematologic toxicity was limiting with 75% of patients experiencing substantial-severe leukopenia. Clinically evident heart failure developed in one patient; in three other patients there was minor-moderate alteration of cardiac function during mitoxantrone-cyclophosphamide therapy. Based on these data, it is believed that this regimen may provide significant long-lasting palliation in patients with advanced breast cancer.

Introduction

In patients with metastatic breast cancer, treatment with single agents results in response rates varying from about 20 to 35% (1). Responses to single agents, however, are rarely complete and often of short duration.

Doxorubicin is currently considered the most active drug (2), followed by alkylating agents, in particular cyclophosphamide.

Mitoxantrone (Novantronc® dihydroxyanthra-cene-dione) is a new substituted anthraquinone with marked antitumor activity in mouse tumor systems (3), as well as in human tumors, including breast cancer (4). Its efficacy in patients with breast cancer, as defined by several phase II studies, is comparable with that of other single agents, including doxorubicin (4–6). Mitoxantrone is well tolerated. Leukopenia is usually the only dose-limiting toxic effect; low incidence of other types of toxicity (e.g. nausea, vomiting and alopecia) is reported (7, 8). In particular, the observation that cardiotoxicity is less frequent after mitoxantrone than after doxorubicin treatment (9) has led us to propose the possible substitution of mitoxantrone for this anthracycline in combination regimens.

It is generally recognised that multiple agents are more effective than single agents, at least with respect to response rates and especially to complete responses. Combinations including doxorubicin and cyclophosphamide are among the most widely used (10, 11).

These data prompted us to investigate a
mitoxantrone-cyclophosphamide combination as first-line treatment of patients with advanced breast cancer. The aims of this multicenter study were to determine the response rate, duration of response, and to evaluate the toxicity of this combination regimen with special attention to cardiotoxicity.

**Patients and methods**

**Patients**

Patients with locally advanced or metastatic breast cancer, seen at participating institutions were entered into this clinical trial. Eligibility criteria for entry into this study included histologically confirmed breast cancer with evaluable or measurable disease, WHO performance status of at most 2 and an expected survival of at least 6 weeks. A leukocyte count $\geq 4000/\text{m}^3$ and/or platelet count $\geq 100,000/\text{m}^3$, serum bilirubin and creatinine $\leq 2.0 \text{mg/dl}$ and a normal cardiac function were also required. No patient was disqualified on the basis of previous radiotherapy and/or endocrine therapy. Previous curative or adjuvant chemotherapy within the last two years or presence of brain metastases precluded patient eligibility for the study. Single informed consent was obtained, according to institutional policy.

Pretreatment evaluation included a complete history and physical examination, full blood counts, blood chemistry including serum creatinine and bilirubin, urinalysis, ECG, chest X-rays and appropriate radiographs and scintiscans for measurement of disease. Full blood counts and ECG were repeated every week after treatment, the remaining, every 3–4 weeks prior to each treatment.

**Treatment**

Cyclophosphamide (Endoxan®, Asta; 600 mg/m²) was infused i.v. over 30 minutes on day 1, and mitoxantrone (Novantrone®, Cyanamid Lederle; 16 mg/m²) was infused over 30 minutes on day 2. Drug administration was repeated every 3–4 weeks, according to toxicity, and continued until the development of progressive disease, or for a maximum of 12 cycles. Due to substantial severe leukopenia occurring in most patients at 16 mg/m², mitoxantrone dose was decreased to 12–14 mg/m² for the last 13 patients.

Toxicity was graded according to WHO criteria (12). The dose of both drugs was reduced according to clinical judgement, if grade 1–2 toxicity was reached (leukocyte counts between 4000 and 2000/ mm³, and/or platelet counts between 100,000 and 50,000/mm³). Mitoxantrone was reduced in steps of 2 mg/m². No drugs were given if grade 3–4 toxicity occurred (leukocyte counts less than 2000/ mm³ and/or platelet counts less than 50,000/mm³).

Assessment of response was performed using standardised response criteria. In brief, complete response was defined as the disappearance of all clinical evidence of active tumor for at least 4 weeks. A partial remission was defined as a 50% or greater decrease in the sum of the products of the diameters of all measurable lesions, without the appearance of new lesions, for at least 4 weeks.

**Results**

**Patient characteristics**

From August 1982 to November 1983, 32 patients were entered into this study. Patient characteristics are listed in Table 1. Two patients were premenopausal and 30 were postmenopausal. Their mean age was 55.3 years (range 36–73). The mean performance status was 0.7 (range 0–2). The mean duration of disease was 47.6 months, with a range of 0 to 168 months.

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<tr>
<th>Table 1. Characteristics of the patients.</th>
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<td>Number of patients</td>
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<td>Mean performance status (WHO) (range)</td>
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<td>Mean duration of disease, months (range)</td>
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