Anti-Cancer Drugs, 3, pp. 471–473

Salvage chemotherapy with mitoxantrone and mitomycin with or without methotrexate in advanced breast cancer

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Thirty-three patients with advanced and refractory breast cancer were treated with two mitoxantrone-containing regimens (mitoxantrone plus mitomycin and mitoxantrone plus mitomycin plus methotrexate). All patients had received previous chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF); cyclophosphamide, adriamycin and fluorouracil (CAF); or CMF and CAF. Partial response occurred in five patients (15 ± 12%), stable disease occurred in 15 patients (45 ± 17%) and progressive disease occurred in 13 patients (40 ± 17%). The median duration of response was 5 months. The median actuarial survival was 11 months. Toxicity was mild, even in patients who had previously received anthracyclines; generally it was mainly hematological. We thus recommend mitoxantrone-containing regimens as salvage chemotherapy in advanced breast cancer.

Key words: Breast cancer, methotrexate, mitomycin, mitoxantrone, salvage chemotherapy.

Introduction

Mitoxantrone is an anthracenedionic analog which is particularly active, alone or in combination with other drugs, in the adjuvant or palliative treatment of breast cancer.

In advanced disease it has been employed in association with several drugs; its association with cyclophosphamide and fluorouracil (CNF) has an activity comparable to anthracycline-containing associations or to cyclophosphamide, methotrexate and fluorouracil (CMF).[1,2]

The combination mitoxantrone, mitomycin and methotrexate (MMM) has already been tested in patients who had not previously received chemotherapy, and gave a response rate of 47%.[3] In a randomized study with 86 patients, MMM showed an efficacy and toxicity similar to CMF.[4]

A partial response rate of 45% was also observed with a combination of mitoxantrone, prednimustine and fluorouracil administered as first and second line chemotherapy.[5] In previously treated patients, however, some discouraging results with a combination of mitoxantrone and mitomycin (MM) have recently been reported.[6]

In our study we evaluate a combination of mitoxantrone and mitomycin with or without methotrexate as salvage chemotherapy in patients with advanced breast cancer previously treated with first or second line chemotherapy.

Patients and methods

Thirty-three patients with advanced, histologically proven, breast cancer entered the study. Eligibility criteria were: advanced, measurable or evaluable disease; life expectancy of at least 3 months; no brain metastases; normal liver, cardiac and renal functions; WBC $>3500/mm^3$; and platelets $>100\,000/m^3$.

All patients had received previous chemotherapy with: CMF, 16 cases; cyclophosphamide, adriamycin and fluorouracil (CAF), 14 cases; and CMF and CAF, three cases. Fourteen patients had previously received tamoxifen. All patients had progressive disease during first or second line chemotherapy. The median age was 58 years. Eight patients were pre-menopausal and 25 were post-menopausal. ECOG performance status was: 0, 11 cases; 1, nine cases; 2, eight cases; and 3, five cases. Metastases involved bone (18 cases); soft tissue (20 cases); lung (13 cases); liver (eight cases); and abdomen (three cases). No patient had brain metastases.

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Table 1. Toxicity in 150 cycles of chemotherapy

	WHO grade toxicity (%)				
	0	1	2	3	4
Anemia	13	75	10	2	—
Leukopenia	3	5	70	20	2
Thrombocytopenia	32	60	8	—	—
Stomatitis	90	10	—	—	—
Diarrhea	95	5	—	—	—
Nausea/vomiting	53	35	12	—	—
Alopecia	40	35	25	—	—
Heart	100	—	—	—	—

The treatment consisted of mitoxantrone (8 mg/m^2, i.v.) on day 1 and 21, and mitomycin C (8 mg/m^2, i.v.) on day 1 (MM). Cycles were repeated every 6 weeks. Patients who had not received methotrexate in the previous chemotherapy (14 cases) also received methotrexate (40 mg/m^2, i.v.) on day 1 and 21 (MMM). WHO criteria of response and toxicity were employed. All patients had measurable or evaluable disease. Pleural effusions, ascites and osteolytic bone metastasis were considered evaluable disease.

Results

Results were evaluated in all patients in terms of response rate, survival and toxicity. A total of 150 courses were administered with a median of five courses (range 1–9). Partial response occurred in five patients (15 ± 12%), stable disease occurred in 15 patients (45 ± 17%) and progressive disease occurred in 13 patients (40 ± 17%). The median duration of response was 5 months. The median actuarial survival was 11 months. Toxicity was mainly hematological with leuko-thrombocytopenia WHO grade 3–4 seen in only 22% of cycles. Gastrointestinal side effects were mild; cardiac damage and WHO grade 3 hair loss were not registered (Table 1). No treatment-related death occurred.

Discussion

Mitoxantrone is an effective drug in breast cancer and is employed in the early stages of breast cancer as either neoadjuvant therapy or adjuvant regimen.[7]

Our experience concerns the treatment of refractory, advanced breast cancer with two mitoxantrone-containing regimens (MM versus MMM). Despite pretreatment, toxicity was mild and mainly hematological, even in patients who had previously received anthracyclines. The limited number of cases does not allow us to define whether the two schedules employed have different therapeutic activity or toxicity. As all patients in our series were pretreated, the overall response rate and survival obtained deserve favorable consideration from a clinical point of view.

Recently, discouraging data have been reported with a MM combination in a group of 43 patients.[6] A higher percentage of patients in this previous series was pretreated with anthracyclines than in our study (29/43 versus 17/33). Moreover, in our study, out of 17 patients, 14 who had previously received adriamycin were treated with a three-drug combination containing methotrexate in addition to MM. These differences in patient characteristics and in chemotherapy could explain the discrepancy between our study and that of Repetto *et al.*[6] Other differences, however, could also be involved.

Conclusion

We recommend mitoxantrone-containing regimens as salvage chemotherapy in advanced breast cancer. It is possible that anthracycline pretreatment influences the outcome of this salvage chemotherapy; its relevance should be evaluated in further studies. The role of methotrexate in mitoxantrone-containing regimens could be explored in a randomized trial. Finally, because the dose-limiting toxicity of mitoxantrone is hematological, the drug,

alone or in combination, could be explored in escalating dose with granulocyte macrophage colony stimulating factor rescue or bone marrow transplantation[8] in advanced breast cancer.

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(Received 20 July 1992; accepted 12 August 1992)