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SHORT COMMUNICATION

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Clinical effects of combination therapy with mitoxantrone, vincristine, and prednisolone in breast cancer

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Abstract *Purpose*: We assessed the clinical efficacy and safety of mitoxantrone hydrochloride which has been used as an anticancer drug in our hospital to treat breast cancer patients since 1993. *Methods*: A group of 23 patients with breast cancer were given one course of the following regimen every 3 weeks: mitoxantrone hydrochloride (8 mg/m^2 i.v. day 1), vincristine sulfate (1.2 mg/m^2 i.v. day 1), and prednisolone (30 mg orally days 1–7). *Results*: The response rate was 52.2% including a complete response in four patients, and a partial response in eight patients. Adverse drug reactions included leukocytopenia (78.3%, 18/23 patients), alopecia (30.8%, 7/23), and peripheral neuropathy and generalized fatigue (26.1%, 6/23). In patients responding to the drug regimen, 50% survival was 29 months, and in those not responding it was 12 months. *Conclusion*: Combination treatment with mitoxantrone hydrochloride, vincristine sulfate and prednisolone is an effective treatment for breast cancer.

Keywords Recurrent breast cancer · Mitoxantrone · Vincristine · Prednisolone

Introduction

We sometimes see patients with recurrent breast cancer resistant to treatment with cyclophosphamide/doxorubicin/fluorouracil (CAF). Since 1993, we have been using mitoxantrone hydrochloride (MIT), an anticancer drug of the anthraquinone class, as second-line chemotherapy because MIT, similar to doxorubicin, inhibits synthesis of DNA and RNA without showing complete cross-resistance with doxorubicin. Thus, in the present study, we further examined the clinical efficacy of MIT in breast cancer patients.

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Patients and methods

The patients were 23 women with breast cancer (mean age 55.3 years) including 3 without previous treatment, 11 who had received adjuvant chemotherapy, 1 who had received preoperative chemotherapy, and 8 who had received intensive chemotherapy to prevent recurrence. We included previously untreated patients since the aim of the present study was to find an effective second-line chemotherapy. Of these 23 patients, 18 were given anthracycline anticancer drugs. The lesions evaluated, including multiple cases, were: soft tissue in ten patients, lymph node recurrence in nine, bone metastasis in eight, lung metastasis in four, and liver metastasis in one. The mean number of cycles was 3.9 and follow-up periods were from 8 to 92 months. The details of the study population are presented in Table 1. Written informed consent was obtained from all patients. They had been advised about adverse reactions because they had completed a phase I trial at that time.

The treatment regimen comprised 8 mg/m^2 MIT i.v. on day 1, 1.2 mg/m^2 vincristine sulfate i.v. on day 1, and 30 mg prednisolone orally on days 1–7. This regimen was given once every 3 weeks.

Patient responses were judged according to the rules of the Japanese Breast Cancer Society [1]. The effects were evaluated by CT of the lung, liver and lymph nodes, and by direct measurement in two directions as for skin lesions. The effect on bone metastasis was evaluated by MRI, with calcification of osteolytic lesions and bone scintigram as references.

Results

The clinical results included four complete responses, eight partial responses, seven no change, three progressive disease, and one not evaluated. The response rates were 52.2% (12/23 patients) in total, including 61.5% (8/13 patients) who underwent initial treatment, and 40.0%

Table 1 Study population

Total number of patients	23
Metastatic disease	
One	12
Two	11
Hormonal receptor	
Positive	9
Negative	10
Unknown	4
Time to recurrence (years)	
< 1	11
1–5	10
> 5	2

Table 2 Responses among 23 evaluable patients

Complete response	4
Partial response	8
No change	7
Progressive disease	3
Not evaluated	1
Response rates	
Overall	12/23 (52.2%)
First line	8/13 (61.5%)
Second line[a]	4/10 (40.0%)

[a]A high efficacy was also seen in second-line treatment patients

Table 3 Toxicity according to NCI-CTC criteria

Toxicity	Grade				No. (%) of patients ($n = 23$)
	1	2	3	4	
Blood/bone marrow					
Hemoglobin	1	2	0	0	3 (13.0)
Leukocytopenia	4	5	7	2	18 (78.3)
Cardiovascular[a]					
Ventricular arrhythmia	0	0	1	0	1 (4.3)
Cardiac ventricular function	0	0	1	0	1 (4.3)
Constitutional					
Fatigue	1	5	0	0	6 (26.1)
Fever	1	0	0	0	1 (4.3)
Dermatological					
Alopecia	4	3	0	0	7 (30.4)
Gastrointestinal					
Anorexia	2	1	2	0	5 (21.7)
Nausea	1	4	0	0	5 (21.7)
Vomiting	1	0	0	0	1 (4.3)
Neurological					
Neuropathy-sensory	0	6	0	0	6 (26.1)

[a]In the two patients with serious toxicities of the circulatory system it was not possible to continue treatment

(4/10 patients) who received the second-line treatment (Table 2). Among the responding patients, 3-year survival was 47.6% and 5-year survival 19.0%, and 50% survival was 29 months. The median survival time was 24.7 months.

Side effects, including multiple incidences, were mainly leukocytopenia (78.3%, 18/23 patients), followed by alopecia (26.1%, 6/23), peripheral neuropathy (17.4%, 4/23), gastrointestinal symptoms (13.0%, 3/23), and cardiovascular events (4.3%, 1/23) (Table 3).

In conclusion, MIT showed high response rates in patients receiving the drug as an initial treatment and also showed efficacy in patients previously treated with anthracyclines. This suggests that MIT is effective as second-line chemotherapy.

Discussion

As a chemotherapeutic, doxorubicin has strong activity against breast cancer, and the response rates to CAF combined therapy are reportedly 40–70% [2]. However, a second-line chemotherapy has been needed for patients resistant to doxorubicin treatment. To cope with this, we have been using MIT, an anthraquinone anticancer drug that shows an antitumor mechanism similar to that of doxorubicin, i.e. inhibition of DNA and RNA synthesis. In 1993, we employed MIT, which has a similar but greater efficacy to doxorubicin and is less toxic to the cardiovascular system. Although response rates to MIT alone are approximately 23% [3], the drug shows synergistic action with other drugs, e.g. vincristine sulfate [4]. In the present study, the high response rate to the drug regimen including MIT supposedly resulted from the synergistic effect of the other two drugs, vincristine and prednisolone. Prednisolone has been more commonly used in chemotherapy in Japan than prednisone. The high response rate to the regimen in patients previously treated with anthracycline drugs could be considered to be due to a limited cross-resistance between the combined drugs. In general, prednisolone sulfate has been used concomitantly with MIT to increase antitumor effects and to decrease adverse drug reactions, and the combination regimen used in the present study has been shown to reduce adverse drug reactions [5].

The drug regimen used in the present study caused the side effects of leukocytopenia, peripheral neuropathy and cardiovascular events. Most of the leukocytopenia could be treated with granulocyte colony-stimulating factor, but it was a dose-limiting factor in four patients. Patients showing cardiovascular events and ventricular premature beats were admitted for treatment, and therefore could not remain in the study. Peripheral neuropathy due to vincristine sulfate was transient.

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