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A combination chemoendocrine therapy of mitoxantrone, doxifluridine, and medroxyprogesterone acetate for anthracycline-resistant advanced breast cancer

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Abstract Between January 1993 and October 1995, 34 patients with anthracycline-resistant advanced breast cancer were treated with a combination chemoendocrine therapy of mitoxantrone (MIT), doxifluridine (5′-DFUR) and medroxyprogesterone acetate (MPA). Of 34 patients, 28 were evaluable for efficacy of this combination therapy, and 30 including 2 for whom data were incomplete were assessed for adverse drug reactions. Adriamycin (ADM) was used for pretreatment in 12 patients, 4′-epi-ADM in 6, and THP-ADM in 12. In the eligible patients, 8.0 mg/m^2 MIT was administered intravenously every 4 weeks, and 600 mg MPA and 600 mg 5′-DFUR were given orally every day. The median follow-up period was 25 weeks (range 2–90 weeks). The median cumulative dose of mitoxantrone was 66 mg (range 12–121 mg). Of the 28 patients, 11 (39.3%) responded to this combination therapy. As for response in relation to predominant site of lesion, 1 of 5 soft tissue lesions (20%) and 8 of 12 bone metastases (66.7%) showed a partial response, and one complete response and one partial response (25.0%) were seen in eight lung lesions. None of three pleural lesions responded to this therapy. The median duration of response was 31 ± weeks (range 12–82 weeks). Adverse drug reactions were controllable or tolerable. Combined chemoendocrine therapy with a low dose of MIT is a well-tolerated and moderately effective regimen for the treatment of anthracycline-resistant advanced breast cancer.

Key words Mitoxantrone · Doxifluridine · Medroxyprogesterone acetate · Anthracycline-resistant advanced breast cancer

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Introduction

It is accepted worldwide that anthracycline-containing chemotherapy regimens are effective for advanced breast cancer [1–7]. However, when the tumor acquires resistance to anthracyclines, it is hard to recommend a subsequent effective treatment [8]. Mitoxantrone (dihydroxyanthracenedione, MIT) is a substituted anthraquinone with a similar spectrum of activity to adriamycin in experimental tumors [9]. MIT is a new active single agent for treatment of previously untreated [10, 11], treated [8, 12, 13], or both untreated and treated patients with advanced breast cancer [14]. Cowan et al. [15] reported the results of a randomized trial showing that the antitumor effect of MIT is similar to that of

adriamycin (ADM). MIT shows activity without total cross-resistance with ADM in animal models [16–18] and in human tumor cloning assays [16–21]. MIT is a new anticancer drug with significant clinical activity [22]. It is well tolerated, with leukopenia being the dose-limiting toxic effect. Alopecia, nausea, and vomiting are uncommon and the incidence of cardiotoxicity is significantly lower than with ADM [15]. MIT is expected to be effective for anthracycline-resistant breast cancer.

Doxifluridine (5′-deoxy-5-fluorouridine, 5′-DFUR) is an anticancer agent synthesized by Cook et al. [23] with less toxicity and immunosuppressive activity than 5-fluorouracil (5-FU) [24]. 5′-DFUR is converted to 5-FU by the pyrimidine nucleoside phosphorylases (PyNPase), thymidine phosphorylase and uridine phosphorlylase, which are found predominantly in humans and rodents, respectively [25, 26, 27]. The former enzyme has been recently shown to be identical to platelet-derived endothelial cell growth factor (PD-ECGF) [28]. Toi et al. [29] have suggested that the expression of PD-ECGF/thymidine phosphorylase plays an important role in the promotion of angiogenesis in human breast cancer.

Recently, medroxyprogesterone acetate (MPA) as well as tamoxifen has been widely used in the treatment of patients with advanced breast cancer [30]. In Japan, oral high-dose MPA has been shown to be an effective treatment for patients with advanced breast cancer as second- or third-line treatment as well as for first-line treatment [31–34]. We have reported that MPA is effective in patients with recurrent breast cancer as second- or third-line treatment, and that MPA might improve the prognosis of those who respond [35]. Myeloprotection and improvement of appetite with the use of MPA contribute to the quality of life (QOL) of patients treated with chemotherapy [31, 33, 34]. Furthermore, the angiostatic activity of MPA has been reported [36]. The antitumor effect may be enhanced by a combination of MPA with 5′-DFUR. Based on the above results, we used a regimen of a low dose of MIT in combination with 5′-DFUR and MPA for the treatment of outpatients with anthracycline-resistant-resistant advanced breast cancer.

Patients and methods

Patient characteristics

Table 1 shows the patient characteristics. A total of 34 patients with advanced breast cancer entered this study, of whom 28 were evaluable for efficacy of the combination therapy, and 30 including 2 for whom data were incomplete were assessed for adverse drug reactions. The median age was 55 years (range 37–76 years); 10 patients were under 50 years, and 18 were 50 years and over. Nine patients were premenopausal and 19 were postmenopausal. Five patients had stage IV breast cancer and 23 had recurrent disease. The tumors were estrogen receptor positive in 18 patients and negative in 5, and of unknown status in 5. Predominant metastatic sites consisted of 5 soft tissues, 12 bone, 8 lung, and 3 pleural. Seven patients had previously received radiation and 25 had received endocrine therapy (antiestrogen and/or MPA). All patients (12 treated with ADM, 6 with 4′-epi-ADM and 12 with THP-ADM) had been previously treated with anthracyclines for active disease and then progressed. The total dose of ADM ranged from 160 to 500 mg (median 312 mg), of 4′-epi-ADM from 120 to 900 mg (median 340 mg) and of THP-ADM from 60 to 720 mg (median 215 mg) (Table 2). Two patients received two of the three anthracyclines.

Table 1 Patient characteristics

	No. of patients
Evaluable patients	28
Age(years)	
Median (range) 55 (37–76)	
< 50	10
≥ 50	18
Menopausal status	
Premenopausal	9
Postmenopausal	19
Stage IV	5
Recurrence	23
Estrogen receptor status	
Positive	18
Negative	5
Unknown	5
Predominant metastatic sites	
Soft tissue	5
Bone	12
Lung	8
Pleura	3
Previous therapy	
Radiation	7
Endocrine therapy	25
Tamoxifen	21
Toremifene	1
3-Hydroxytamoxifen	1
Medroxyprogesterone acetate	15
Chemotherapy	28
Adriamycin	12
4′-Epi-adriamycin	6
THP-adriamycin	12

Table 2 Median dose of anthracycline

Anthracycline	Median dose (range)	No. of patients
Adriamycin	312 mg (160–500 mg)	12
4′-Epi-adriamycin	340 mg (120–900 mg)	6
THP-adriamycin	215 mg (60–720 mg)	12

Treatment schedule

The treatment was usually performed on an outpatient basis. All patients provided written informed consent before they received treatment. The treatment schedule is shown in Table 3. MIT was administered intravenously at a dose of 8.0 mg/m^2 every 4 weeks. A total of 600 mg 5′-DFUR and 600 mg MPA were given orally every day. Patients generally received 8 mg dexamethasone on day 1 to prevent adverse drug reactions. Washout periods from previous treatments were at least 4 weeks for the anthracyclines, and at least 2 weeks for the mild chemotherapy or endocrine therapy.

Table 3 Treatment schedule

Mitoxantrone	8 mg/m^2	Intravenous	Day 1
Medroxyprogesterone acetate	600 mg	Oral	Days 1–28
5′-Deoxy-fluorouridine	600 mg	Oral	Days 1–28

Table 4 Response to a combination therapy with mitoxantrone (median dose 66 mg, range 12–121 mg)

No. of patients	Complete response	Partial response	No change	Progressive disease	Response rate
28	1	10	6	11	39.3%

Criteria for assesment of response to treatment

The therapeutic response to the combination therapy was evaluated according to the protocol guidelines on clinical assessment of response to therapy in advanced breast cancer of Japanese Breast Cancer Society [37]. Of the 34 patients with advanced breast cancer, 28 were available for evaluation. Of the remaining six patients, four were ineligible and data were incomplete for the other two. Of the four ineligible patients, three were ineligible because of insufficient washout periods from previous therapy and one as a result of grade 2 thrombocytopenia. The other two patients were unevaluable because of a lack of observation records for their lesions. The criteria for deciding the response to treatment were as follows: *complete response* (*CR*) tumors disappeared completely for more than 4 weeks, and no new lesions appeared; *partial response (PR)* a decrease in tumor size of more than 50% continued for more than 4 weeks, and no new lesions appeared (for the bone metastases, osteoblastic changes appeared in the osteolytic lesions and continued for more than 4 weeks); *no change (NC)* a decrease of up to 50% or a less than 25% increase in tumor size continued for more than 4 weeks, and no new lesions appeared (for bone metastases, the above results continued for more than 8 weeks); *progressive desease (PD)* an increase in tumor size of more than 25% or the appearance of new lesions. The response rate was calculated as the number of responders (CR and PR)/total number of patients × 100. The grade of adverse drug reactions was assessed according to a modification of the WHO criteria [38].

Results

The median follow-up period of this study was 25 weeks (range 2–90 weeks). The median cumulative dose of MIT was 66 mg (range 12–121 mg). Of the 28 evaluable patients, 11 (39.3%) responded to the combination therapy (Table 4). As for response in relation to predominant site of lesion, 1 of 5 soft tissue lesions (20.0%) and 8 of 12 bone metastases (66.7%) showed a PR, and 1 CR and 1 PR (25.0%) were shown in 8 lung lesions. None of 3 pleural lesions responded (Table 5). The median time to response was 10 weeks (range 4–35 weeks) and the median duration of response was 31^{+}_{-} weeks (range $12–82^{+}_{-}$ weeks; Fig. 1). Adverse drug reactions are shown in Table 6. One patient showed grade 3 anorexia, which recovered without any supportive treatment. Alopecia (grades 1 and 2) was observed in nine patients (30.0%). Weight gain and/or fluid retention (presumably due to MPA) were not observed during the study period. Myelosuppression was the most frequent abnormal laboratory finding. Of 30 patients, 25 (83.3%) showed leukopenia, and 4 showed grade 4 leukopenia, but these 4 patients recovered without G-CSF (granulocyte colony stimulating factor) treatment, and febrile neutropenia was not seen. No cardiac toxicity was observed with this total dose of MIT.

Discussion

Combination treatments with MIT have been reported to give a higher response rate as first-line treatment (38% [39], 47% [40]), as first-line or second-line treatment (65% [41], 50% [42], 28% [43]) and as second-line treatment (45% [44]) compared with a single MIT treatment. The response rate of patients who had or had not received previous ADM treatment was 38% and 69%, respectively. Patients who had not received

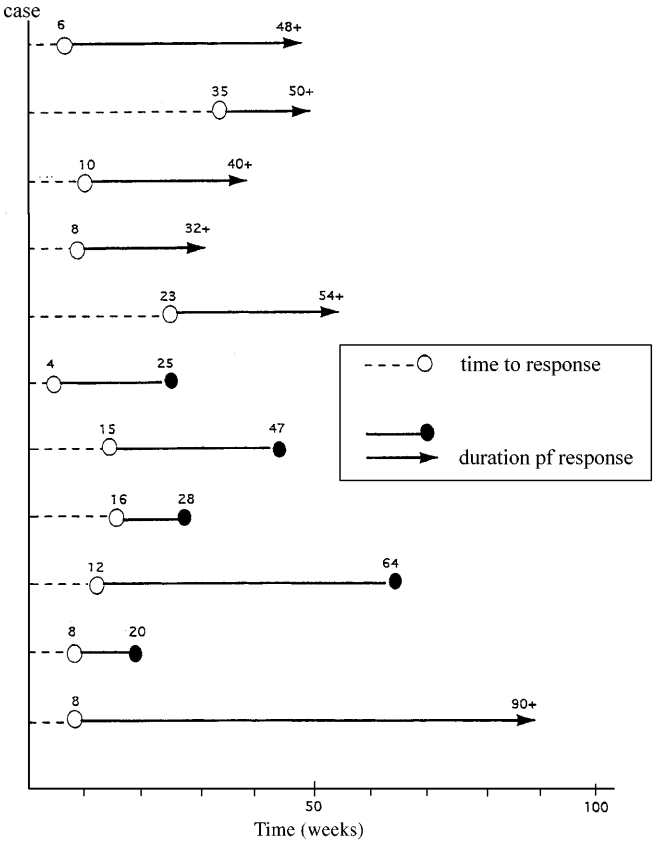

Fig. 1 Time to response and duration of response

Table 5 Response in relation to site of lesion

Metastatic site	*n*	Complete response	Partial response	No change	Progressive change	Response rate
Soft tissue	5	0	1	1	3	20.0%
Bone	12	0	8	2	2	66.7%
Lung	8	1	1	2	4	25.0%
Pleura	3	0	0	1	2	0.0%

Table 6 Adverse drug reactions

	n	Grade 1	2	3	4	Rate (%)
Anorexia	3	2		1		10.0
Nausea/vomiting	4	3	1			13.3
Fatigue	6	5	2			20.0
Stomatitis	1	1				3.3
Alopecia	9	7	2			30.0
Fever	2	2				6.7
Leukocyte	25	3	7	13	4	83.3
Platelet	4	3	1			13.3
Hemoglobin	3		2	1		10.0
GOT	3	1	2			10.0
GPT	3	1	2			10.0
ALP	2	2				6.7

anthracyclines had a 42.1% response rate compared with 15% in patients who had received anthracyclines. Wallace et al. [17] have demonstrated that MIT and ADM show partial cross-resistance against experimental tumors in mice. Therefore, the response rates to combined MIT treatments, including those in this study, are not so low despite previous ADM treatment. In prescribing a combination chemotherapy regimen, the most important issue is how to select the agents to be combined and how to decide the dose of each agent. Combination chemotherapy with anthracyclines is well known to be effective for advanced breast cancer. However, it is difficult to find a subsequent effective treatment for anthracycline-resistant breast cancer. MIT was selected as the main agent of the subsequent combination treatment because of its expected effectiveness against anthracycline-resistant tumors. Although the recommended dose of MIT for breast cancer is from 8 to 14 mg/m^2, we chose a low dose of MIT (8 mg/m^2) to be administered once every 4 weeks because the subsequent treatment should be chiefly performed on an outpatient basis in consideration of the QOL of the patients..

5′DFUR is an oral drug which is converted to 5-FU by PyNPase. In the treatment of breast cancer using 5′-DFUR, a response rate of 35.9% has been reported in a phase II trial in Japan [45]. A low dose (600 mg) of 5′DFUR was given every day in this regimen.

MPA has both an antitumor effect and an anabolic steroid action [30–35]. This anabolic action gives patients the nutritional benefit of improvement in appetite, [46, 47], and the benefits of greater myeloprotective activity, and of increases in serum thyroid binding prealbumin and retinol-binding protein [46]. A low dose (600 mg) of MPA was administered orally every day so as not to induce severe weight gain. The combination of MPA and 5′-DFUR may be a new strategy for the treatment of breast cancer because MPA has an antiangiogenic activity, and the expression of PDECGF/thymidine phosphorylase plays an important role in the promotion of angiogenesis and is a marker of effectiveness of 5′-DFUR treatment.

Myelosuppression (leukopenia) is one of major toxicities of MIT [8–15]. The most frequent nonhematological toxicities are nausea and vomiting, but they are rarely severe [11]. Moderate hair loss has been reported as a side effect [12]. The incidence of cardiotoxicity is lower with MIT than with ADM [15]. Our low-dose MIT combination treatment resulted in low rates of gastrointestinal toxicity and alopecia. Cardiotoxicity was not seen during the observation period. The low frequency of side effects with this regimen are also benefits for the QOL of patients. The clinical value of this regimen is that it is effective for anthracycline-resistant breast cancer and can be used safely on an outpatients basis.

We conclude that the combination therapy of MIT, 5′-DFUR, and MPA is an effective, well-tolerated regimen for anthracycline-resistant stage IV or recurrent breast cancer when a limiting dose of MIT is considered.

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