Recurrent Breast Cancer Treated Successfully with Mitomycin-C and Vinblastine after Failure of Both Doxorubicin-containing Regimen and Paclitaxel — A Case Report —

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SEKINE, I., SASAKI, Y., FUJII, H., OHTSU, T., WAKITA, H., IGARASHI, T., ITOH, K. and ABE, K. *Recurrent Breast Cancer Treated Successfully with Mitomycin-C and Vinblastine after Failure of Both Doxorubicin-containing Regimen and Paclitaxel — A Case Report.* Tohoku J. Exp. Med., 1996, 178 (3), 331-337 — Cross-resistance is one of the chief obstacles in salvage therapy for refractory breast cancer. Although paclitaxel is one of the most promising drugs, it shows a response rate of 30% at most for patients with breast cancer resistant to doxorubicin, and no effective treatments for tumors refractory to both agents have been reported. We describe a 38-year-old woman with recurrent breast cancer, who was treated successfully with mitomycin-C and vinblastine after doxorubicin-based chemotherapy and paclitaxel failed. The combinations of mitomycin-C and microtubule inhibitors including vinca alkaloids and taxanes may have a potential application to refractory breast cancer. ——— drug resistance; salvage; second line; microtubule inhibitor

The incidence of breast cancer has been recently rising in Japan and the mortality rate reached 11.3 per 100,000 population in 1994, which was three times higher than that in 1960 (Statistics and Information Department 1994). About 40% of the patients with breast cancer in Japan are required to receive systemic therapy because of recurrence or distant metastasis at the initial diagnosis (Koyama et al. 1993; Miura 1993). Moreover, even a doxorubicin-based regimen, which is the standard chemotherapy for metastatic or recurrent breast cancer, has failed to extend survival, and metastatic breast cancer remains incurable (Haller et al. 1991).

Second line chemotherapy has been widely investigated. Paclitaxel is one of

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the most promising drugs for patients refractory to doxorubicin (DOX) (Seidman et al. 1995). However, there are no reports on therapy for patients refractory to both DOX and paclitaxel.

Mitomycin-C (MMC) and vinca alkaloids are considered important salvage chemotherapy for refractory breast cancer because they are approximately 40% non-cross-resistant with other drugs including anthracyclines (Konits et al. 1981). We report a patient with metastatic breast cancer refractory to endocrine therapy, doxorubicin-based chemotherapy and paclitaxel, who was successfully treated with MMC and vinblastine (VLB).

CASE REPORT

A 38-year-old woman with metastatic breast cancer refractory to conventional doxorubicin-containing chemotherapy was referred to the National Cancer Center Hospital East in February 1993. She first noticed a firm lump in the right breast while nursing her baby in January 1985. Breast cancer was diagnosed and right radical mastectomy was performed on July 29, 1985. Histological examination of the specimen revealed invasive ductal carcinoma (scirrhous carcinoma), and was negative for estrogen receptor. Both doxifluridine and tamoxifen were administered orally as adjuvant therapy for 12 months in daily doses of 400 mg and 30 mg, respectively.

At the end of June 1992, she began to complain of pain in the right anterior chest wall. Local and distant recurrences were found with bilateral multiple pulmonary metastases. Beginning in August, she was treated with 30 mg of tamoxifen and a combination chemotherapy of cyclophosphamide (CPM) 400 mg/m², DOX 40 mg/m², 5-fluorouracil (5-FU) 400 mg/m² and methotrexate (MTX) 25 mg/m² repeated for 5 cycles at 4-week intervals. A chest x-ray film in January 1993 showed disease progression.

She was admitted to our hospital in March 1993. No metastasis was detected by CT scan of the head, scintigram of the bone and ultrasound scan of the abdomen. Written informed consent being obtained from the patient, she was registered in a phase II study of paclitaxel for breast cancer and treated with 150 mg/m² intravenously over 24 hr. Since two more cycles repeated at 3-week intervals revealed no objective response, medroxyprogesterone acetate was given orally in a daily dose of 600 mg since June.

She was readmitted in July because of multiple brain metastases. A total dose of 40 Gy during 4 weeks was given to the whole brain and 56 Gy during 5 weeks to the chest wall to relieve pain from the locally recurrent lesion.

In September 1993, cough, sputum, mild dyspnea and back pain developed, and a chest x-ray revealed aggravation of pulmonary metastasis (Fig. 1). Multiple bone metastases were found by the bone scintigram. The hematological study showed a white cell count $4,600 \times 10^9$ /liter, hemoglobin 11.5 g/100 ml and platelet count $314,000 \times 10^9$ /liter. Blood chemistry findings were normal except for an

Fig. 1. Chest x-ray film just before treatment with mitomycin-C and vinblastine revealed bilateral multiple nodules, the largest of which was 6 cm in diameter.

Fig. 2. Chest x-ray film after 2 cycles of mitomycin-C and vinblastine revealed a marked reduction of the nodules both in size and number.

elevated LDH level (2,693 IU/liter). The CEA and CA15-3 were 6.3 ng/ml and 160 U/ml, respectively.

From September 8, 6 cycles of combination chemotherapy of MMC 8 mg/m² (12 mg/body) and VLB 6 mg/m² (9 mg/body) were administered intravenously at 3- to 5-week intervals. The cumulative doses of MMC and VLB were 48 mg/m² (72 mg/body) and 36 mg/m² (54 mg/body), respectively. After 2 cycles of chemotherapy, the pain, cough and dyspnea disappeared completely. Chest x-ray films showed a significant improvement in the metastatic lesions with a 70% decrease in size (Fig. 2). The blood test after the fifth cycle revealed reduced levels of LDH (624 IU/liter), CEA (1.3 ng/ml) and CA15-3 (32 U/ml). Hematological toxicity was mild; the lowest white cell count, hemoglobin and platelet count during the 6 cycles were $1,700 \times 10^9$ /liter, 11.0 g/100 ml and $196,000 \times 10^9$ /liter, respectively. Non-hematological toxicity was not observed.

The chemotherapy was discontinued on January 26, 1994, because disease progression was noted in the locally recurrent site. The overall duration of response to the chemotherapy was 20 weeks. She was well without bone pain or respiratory symptoms until March 23, when she was readmitted because of gait disturbance. A magnetic resonance imaging scan of the head showed aggravation of the brain metastases. She died of the disease on June 27, 1994.

DISCUSSION

The treatment for breast cancer refractory to DOX has not been established. Although paclitaxel is one of the most promising drugs for doxorubicin-resistant tumors, it shows an over all response rate of 30% at most (Seidman et al. 1995). Resistance to paclitaxel is considered to be induced by P-glycoprotein, which results in cross-resistance to vinca alkaloids, anthracyclines, epipodophyllotoxins, and by altered α and β tubulin which have impaired the ability to polymerize tubulin dimers into microtubules. The latter was found in a Chinese hamster ovary cell line resistant to paclitaxel but sensitive to other microtubule inhibitors including vinca alkaloids (Rowinsky et al. 1990).

MMC is considered to have an important role in salvage therapy of breast cancer for the following reasons: 1) a second regimen should not include drugs used previously, and MMC is rarely selected for first line chemotherapy; 2) the mechanisms of resistance to MMC are different from those to DOX or paclitaxel in most cases; 3) MMC monotherapy is effective to some extent in treating patients with tumor resistant to DOX (Legha 1985; Pasterz et al. 1985; Garewal 1988; Yusa et al. 1991). Cumulative myelosuppression lasting for 4 to 5 weeks is one of the most significant side effects of MMC. This may result in a decrease in the final dose intensity and limit its clinical use in heavily treated patients. Vinca alkaloids are another class of drugs with different mechanism of action combined with MMC for salvage therapy, though their efficacy against refractory breast cancer has not been fully evaluated. The combination of MMC and VLB had a

TABLE 1. *Combination of Mitomycin-C and vinblastine for patients with breast cancer refractory to doxorubicin*

Author	Number of patients	Drugs	PR (%)	CR (%)	RR (%)	MDR (months)	MST (months)
Denefrio et al. 1978	14	MMC+VLB	7	0	7	3.7	—
Konits et al. 1981	31	MMC+VLB	37	3	40	4.2	—
Garewal et al. 1983	22	MMC+VLB	32	0	32	5.4	—
Radford et al. 1985	49	MMC+VLB	20	2	22	—	—
Brambilla et al. 1989	44	MMC+VLB	20	3	23	—	—
Navarro et al. 1989	34	MMC+VLB	23	9	32	6.2	—
Sedlacek 1993	22	MMC+VLB	27	0	27	5	7.6
Veronesi et al. 1982	22	MMC+VLB+BCNU	9	0	9	—	—
Zaniboni et al. 1990	29	MMC+VLB+LND	21	3	24	14	12
Kosmidis et al. 1990	22	MMC+VLB+DOX	32	0	32	—	—
	27	MMC+VLB+DBM	22	0	22	—	—
Pierga et al. 1989	53	MMC+VLB+ELP	—	—	28	—	—

PR, partial response; CR, complete response; RR, response rate; MDR, median duration of response; MST, median survival time; MMC, mitomycin-C; VLB, vinblastine; BCNU, carmustine; LND, Lonidamine; DOX, doxorubicin; DBM, dibromodulcitol; ELP, Elliptinum.

response rate of 20 to 40% in patients with advanced breast cancer refractory to DOX. The third drug added to the two agents did not increase the benefit (Table 1).

The patient we described here was treated effectively with MMC and VLB after doxorubicin-based chemotherapy and paclitaxel failed. Although severe side effects were not noted in this case, we should not overlook myelosuppression caused by MMC because the bone marrow function varies with the patients, especially those treated heavily with cytotoxic agents.

Recently, a combination of MMC and navelbine, another microtubule inhibitor, was reported to be effective against doxorubicin-resistant breast cancer (Scheithauer et al. 1993). The combinations of MMC and microtubule inhibitors including vinca alkaloids and taxanes may have a potential application to refractory breast cancer and they are worth investigation in clinical trials.

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