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A CASE OF MULTIPLE BRAIN METASTASES FROM BREAST CANCER RESPONDING TO CHEMOTHERAPY

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Therapies for brain metastasis from breast cancer include surgery, radiotherapy, chemotherapy, and hormonal therapy, used alone or in combination. The therapy selection presents a number of difficult problems, such as complicated recurrence involving other organs, and the presence or absence of multiple brain metastases. In our department during the 15 year period from 1980 to 1994, brain metastasis from breast cancer was seen in 19 cases. The post-treatment survival period we observed was 1～21 months, indicating an extremely poor prognosis.

We reported a case with multiple brain metastases from breast cancer responding to CEF therapy (cyclophosphamide, epirubicin, 5-fuluorouracil) and epirubicin. The patient was diagnosed as phase I breast cancer. Breast-conserving therapy was performed. The estrogen receptor in the tumor was proved to be negative. This report describes a case of recurrent breast cancer with bilateral supraclavicular lymph-node metastases and repeated multiple brain metastases, for which the patient was given repeated chemotherapy and showed a therapeutic effect after each treatment. In the present case, the patient surviving 19 months to date, the cumulative dose of Epirubicin was 2.04 g which far exceeds the maximum acceptable dosage.

This case showed that high-dosed cumulative Epirubicin chemotherapy was effective for multiple brain metastases from breast cancer with negative ER, when careful attention was paid to the cardiac function during the whole course of chemotherapy.

Introduction

The therapeutic performance of recurrent breast cancer has markedly improved in recent years with synthetic treatment, comprised of radiotherapy, chemotherapy and endocrine therapy. However, the prognosis of metastasis from breast cancer is poor, and a number of therapeutic problems remain to be solved, such as metastases in other organs and the presence or absence of multiple brain metastases.

This report describes a case of recurrent breast cancer with repeated supraclavicular lymph node and multiple brain metastases following breast conserving-therapy, for which the patient was given repeated chemotherapy and showed a therapeutic effect after each treatment.

Case Report

Patient: Sixty-year-old female
Chief complaints: Headache, loss of grasping

power of the right hand and dyskinesia in right arm

Anamnesis and family history: Nothing significant

Course of the current disease:

On June 5, 1989, this patient received enucleation of the tumor of 2.0 × 1.5 cm with a tumor-teat distance of 7 cm in the A section of the right breast, under local anesthesia in the out-patient clinic (t=1.3 × 1.3 cm), the tumor was diagnosed as phase I breast cancer (T1N0 M0), and was histopathologically a medullary carcinoma, ly0, v0, ER(−).

On June 23, 1989, a surgical operation was performed under general anesthesia to resect the partial mammary glands (quadrantectomy) and to cleanse the axillary fossae. No axillary lymph node metastasis (n0), or histopathological evidence of residual cancer was detected in the resected specimen. As supplementary postoperative chemotherapy, 5′-DFUR 800 mg was orally administered until Febrary, 1992 (for 2 years and 8 months) (2 consecutive dosing weeks followed by 1 week of withdrawal). No abnormality in tumor markers was noted during this period.

In early April 1992, swelling of right supraclavicular lymph nodes was seen, followed by the left. So the patient visited the out-patient clinic on April 11, 1992. The ultrasonographic findings in the supraclavicular and cervical regions showed an isolated swelling of 3.0 × 1.5 cm in the right breast and multiple lymph-node swellings of 1.5 cm in the left breast. After lymph-node biopsy, the case was diagnosed as that of supraclavicular lymph-node metastasis. The value of tumor marker, TPA, was elevated to 418.9 U/l, while other markers were normal. No pulmonary, hepatic and bone metastases were detected in various examinations.

Six course of CEF therapy (Epirubicin 50 mg, 5-FU 500 mg, CPA 100 mg, p.o.) were applied during the period from April 25, 1992 to July 18, 1992, producing CR effect, and the TPA value normalized. The cumulative dose of Epirubicin was 300 mg at this time. Thereafter, the progress of the disease was followed with the internal use of 800 mg 5′-DFUR. After about 4 months, in November 1992, the swelling of the left supraclavicular lymph node recurred. Therefore, on November 19,1992, supraclavicular fossae were cleansed and cervical lymph nodes were resected, and 2 courses of CEF therapy were applied in the same dose as before. Then single intravenous dose of 50 mg Epirubicin was administered once a month, 9 times in total until November 1993. The cumulative dose of Epirubicin amounted to 850 mg by this time; and, thereafter, only the internal use of 800 mg 5′-DFUR was continued. No abnormality in tumor markers was noted during this period.

Numbness in the digits of the right hand was in early January 1994, and the patient was urgently hospitalized on January 26, 1994 with chief complaints of headache, loss of grasping power in the right hand, dyskinesia in the right arm and dysbasia.

General condition at the time of admission: blood pressure 190/110 mmHg; pulse rate 90/min; rhythmic; no anemia was present in the palpebral conjunctiva; superficial lymph nodes were not palpable;

Neurological findings:

Cranial nerves; No abnormality
Pathologic reflexes; None
Deep tendon reflex; Increased on the right side.
Right upper and lower limbs; Reduced sensation of temperature, touch and pressure, and reduced myodynamia (Barret sign +)
Visual field disturbance; Right homonymous hemianopsia

Hematological findings:

Peripheral blood chemistry; No abnormality
Tumor marker; TPA 150 U/l

CT findings: Four brain metastases were seen in the right frontal, left parietal and occipital regions, with surrounding edema and mass effect. The mid-line structure was displaced to left side. Left Sylvian fissure and lateral ventricle were obliterated.

Immediately after admission, Glyceol at a dose of 600～800 ml/day and Decadoron at a dose of 6～8 mg were administered to treat the brain edema, and the symptoms showed improvement. Then CEF therapy (Epirubicin 70 mg, 5-FU 700 mg, Cyclophosphamide 100 mg, p. o.) was begun on Febrary 4, 1995, and 6 courses of the therapy were administered. In about 5 weeks, numbness in right fingers, headache, loss of grasping power, dyskinesia in the right arm and dysbasia had all improved, and the TPA value normalized. Tumoral images in CT almost completely disappeared, and the case was judged as PR with CR inclination (Fig. 1, 2). Cumulative dose of Epirubicin was 1,270 mg without effect on cardiac function. Thereafter, Epirubicin was given by single intravenous administration at a dose of 70 mg once a month until September 1994, 5 times in total. The

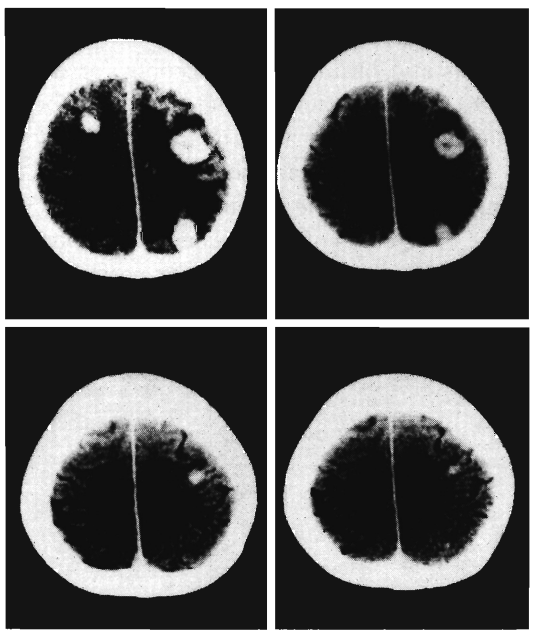

Fig. 1 (Top left) Contrast-enhanced CT scan before chemotherapy reveals a right frontal and two left parietal tumors with surrounding edema. (Top right) After 2 courses of CEF; (Bottom left) after 4 courses of CEF; (Bottom right) after 6 courses of CEF. Two tumors of the three had completely disappeared from the CT scan after 6 courses of CEF.

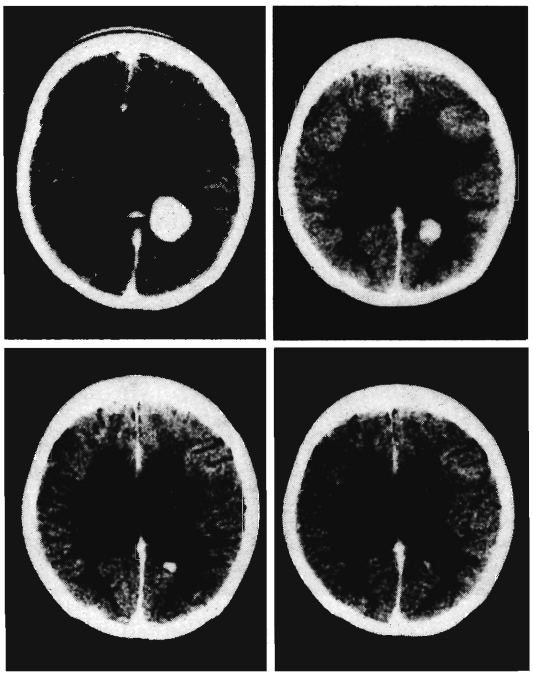

Fig. 2 (Top left) Contrast-enhanced CT scan before chemotherapy reveals a left occipital tumor with surrounding edema. (Top right) After 2 courses of CEF; (Bottom left) after 4 courses of CEF; (Bottom right) CT scan shows that after 6 courses of CEF occipital tumor had almost disappeared.

cumulative dose of Epirubicin by this time was 1,620 mg.

On October 30, 1994, a feeling of heaviness in the head and dysarthria was suddenly experienced, and the patient was uregentaly hospitalized. MRI examination showed metastatic brain tumor in the same region (as before) and different region. Then Glyceol at a dose of 400～600 ml/day and Decadoron at a dose of 4 mg were administered to improve brain edema.

The symptom improved in 2 days, and the CEF therapy (Epirubicin 70 mg, 5-FU 700 mg, CPA 100 mg, p.o.) was begun on September , 1994. Six courses of the therapy were administered. MRI images indicated no tumor and the case was judged as CR (Fig. 3). The cumulative dose of Epirubicin by this time was 2,040 mg.

On March 8, 1995, dyspnea appeared requiring urgent hospitalization. Chest X-ray indicat-

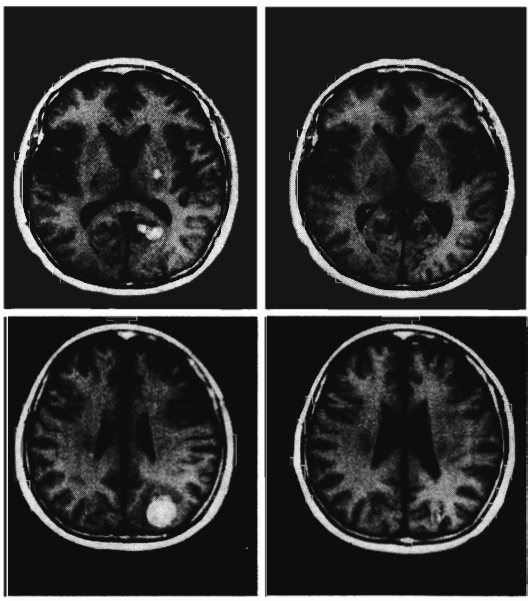

Fig. 3 (Left top and bottom) Contrast-enhanced MRI before chemotherapy reveals left parietal tumors and a left occipital tumor. The MRI on the right top and bottom shows that the tumors completely disappeared after chemotherapy.

ed enlarged cardiac shadow and fluid in the bilateral thoracic cavity (Fig. 3). The results of echocardiography were EF 44%, MR III and PE +. The case was diagnosed as heart failure and given cardiac diuretics. The results of echocardiography performed on April 28, 1995 were EF 54%, MRI and PE ±, and enlarged cardiac shadow and fluid in the bilateral thoracic cavity were eliminated (Fig. 4).

During this period, chemotherapy was suspended. MRI examination was performed because limitation of the movement was observed in both hands which indicated recurrence of the metastatic tumor. The application of chemotherapy including Epirubicin was considered impossible. Therefore, after consultation with the patient and her family, gamma knife therapy was performed on May 2, 1995. Following this treatment, the case was again judged as PR from MRI results (Fig. 5), but the normalization of TPA value and improvement in clinical symptoms were insufficient. We are considering the continued use of the chemotherapy at a low dose.

The complete disease course of this case has been shown in Fig. 6.

Discussion

Metastatic brain tumor accounts for about 10% of all brain tumors, and malignant brain metastasis occurs at an estimated frequency of 15~20%[1]. Brain metastasis from breast cancer occurs at a variable frequency of 2~33%[2)4)]. Out of 1,112 cases of breast cancer experienced in our institution during a 15-year period, brain metastasis was present in 19 cases (only 2% of

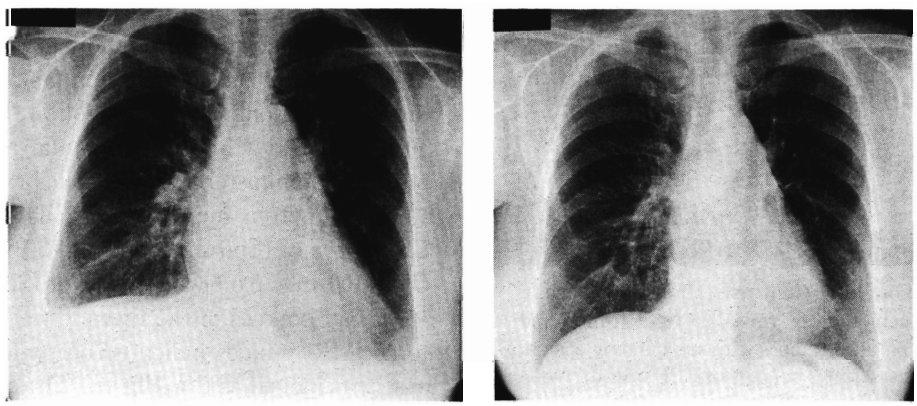

Fig. 4 (Left) Chest X-ray shows cardiomegaly and fluid in the bilateral thoracic cavity. (Right) Chest X-ray shows that cardiomegaly had improved and fluid in the bilateral thoracic cavity had disappeared.

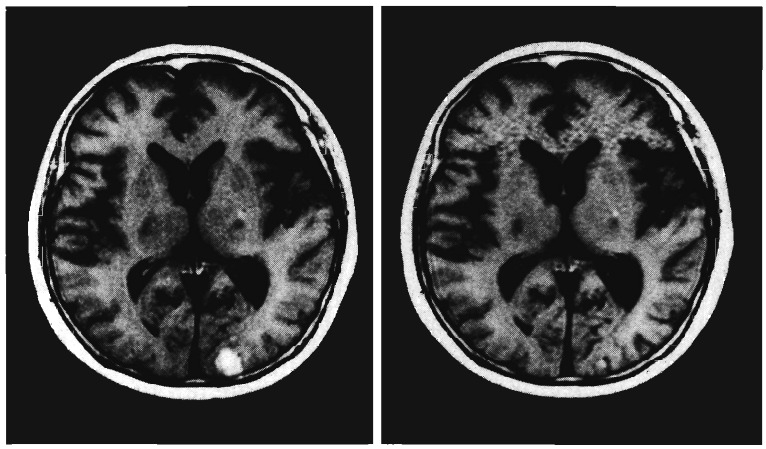

Fig. 5 (Left) Contrast-enhanced MRI before chemotherapy reveals a left occipital tumor. (Right) The tumor had almost completely disappeared after gamma knife therapy.

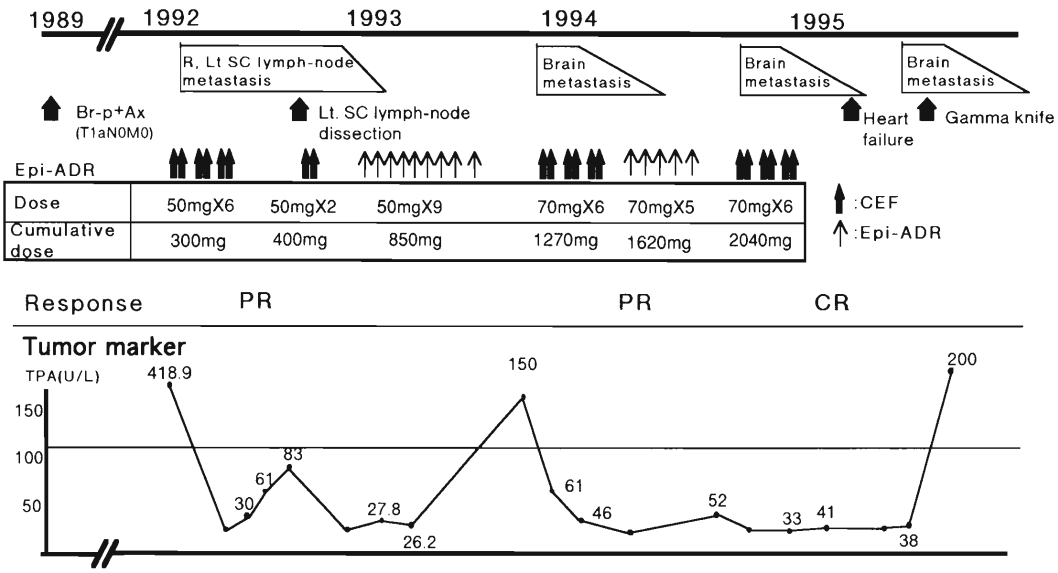

Fig. 6 Clinical course

the total) including 4, 12 and 3 cases of first, second and third recurrences, respectively. However, in consideration of the paucity of the methods of definitive diagnosis and follow up, a higher actual percentage was estimated. Isolated brain metastasis was experienced in only 2 cases (11%). However, an increasing number of cases with isolated metastasis have been seen with the advancement in diagnostic techniques, and reportedly exceeds half of the total number of cases[3].

The treatment of brain metastasis comprised of:

① initial nosotropy (steroids, intracranial hypotensive drugs), ② surgical therapy, ③ radiotherapy, ④ chemoendocrine therapy.

However, there are some difficulties regarding the selection of these therapies, including complicated metastasis involving other organs and the presence of multiple brain metastases.

Among the cases we experienced, chemotherapy was performed on 9 cases, radiotherapy on 4, surgical therapy on 1 and nosotropy on 5. All of these cases resulted in death except for a sole case of brain metastasis, described in this report, who had survived for 19 months to date (chemotherapy + gamma knife therapy).

The survival period after brain metastasis was 4～11 months (mean 7.8 months), 1～21 months (mean 8 months) and 1～2 months (mean 1.6 months for the cases of first, second and third recurrences, respectively, indicating poor prognosis after brain metastasis.

The existence of blood-brain barrier (BBB) places some restrictions on the selection of the chemotherapy regimen of brain metastasis from the breast cancer. However, BBB may not be maintained in the case of brain metastasis and chemotherapy may be effective in such cases.

Rosner et al[5] reported the use of Cyclophosphamide, 5-FU, Methotrexate, Vincristine and prednisolone with an 18～54% efficacy rate, mean 7 months before recurrence, and 31% survival rate for more than 12 months. A report has indicated that the 3-drug concomitant therapy using UFT, CDDP and Aclarubicin is effective for the treatment of brain metastasis from other carcinomas[6].

Tamoxifen is lipid-soluble and easily transferred into the brain tissue. Therefore, it is applicable for the treatment of brain metastatic tumor and has been reported to be in fact useful in the hormone therapy of brain metastasis from breast cancer[7][10] or in endocrine therapy[11][12].

In this case, the estrogen receptor in the tumor was negative, we then performed CEF therapy to our case on bilateral supraclavicular lymph-node metastasis, 34 months after the breast-conserving therapy, and this case entered stage PR. However, recurrence was seen in supraclavicular lymph nodes 4 months later. This case was treated with CEF therapy and surgery, and the metastatic foci disappeared. Thereafter, recurrent multiple brain metastases were seen. Consequently, chemotherapy was repeated, and the terapeutic effect was rated as PR or CR at each treatment schedule.

An anthracycline-group anti-tumor agent, Doxorubicin (DX), frequently causes myocardial disorders and heart failure, when the cumulative dose exceeds 500～550 mg[13]. A DX-derivative, Epirubicin, which has been recently developed to improve the dose-limiting factor, has reportedly less general and chronic toxicity[14][15].

There are few reports on the cumulative dose limit, but Neri et al[16] reported that two patients developed congestive heart failure with Epirubicin at a cumulative dose of 1,200 mg/m^2. In our case, the cumulative dose of Epirubicin was 2,040 mg which was far in excess of the maximum acceptable dose, and the patient did show symptoms of heart failure, which improved with cardiac diuretics. In the recurrence of brain metastasis, it was impossible to use chemotherapy and gamma knife therapy was adopted. It was effective in some of the lesions showing the PR effect, but the clinical symptoms were not adequately improved.

Tjuljandin et al[17] has reported that recently the tolerated dose of Epirubicin has been revised upwards with reported increased response rates. In the present our case, chemotherapy has been extremely effective with slight adverse effects to date, and we are considering the continued use of the chemotherapy at a low dose while maintaining a close watch of the cardiac functions.

In sammary, we reported a case of multiple brain metastases following breast cancer surgery, which was effectively treated with repeated administration of CEF therapy and Epirubicin.

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癌化学療法が奏効した乳癌脳多発転移の1例

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乳癌脳転移に対する治療は放射線療法，化学療法，内分泌療法，手術療法などを単独にまたは組み合わせた集学的治療が行われる．その治療の選択には，他臓器合併再発，多発脳転移巣の有無など，多くの問題点が含まれている．1980年より1994年までの15年間で我々の教室において経験した19例の乳癌脳転移症例の予後について検討すると，脳転移に対する治療後の生存期間は1～21カ月で，極めて予後が悪いことを示した．今回，乳癌術後の多発性脳転移に対してCEF療法とEpirubicinの化学療法が奏効した症例を報告した．患者は病期I乳癌であり，乳房温存療法が施行された．腫瘍のエストロゲンレセプターは陰性である．本症例は乳癌術後に，両側鎖骨上窩リンパ節転移と繰り返し再燃した多発性脳転移に対する化学療法でその都度PR～CRの治療効果が得られ，脳転移後19カ月経過した現在，臨床症状もなく生存している．Epirubicinの総投与量は2.04gにおよび，報告されている心毒性許容量をはるかに越えている．この経験より，ER（－）乳癌の多発性脳転移における化学療法において，心機能に厳重な注意を払えば許容量を越えたEpirubicinの反復投与が可能で，有効であることを報告した．