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Hepatic arterial infusion chemotherapy for liver metastases from breast cancer

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Abstract. Between 1985 and 1992, 56 patients with unresectable liver metastases from breast cancer were treated by repeated hepatic arterial infusion chemotherapy employing an implantable port system. 5-Fluorouracil (5-FU) at 330 mg/m^2 per week, Adriamycin (ADR) at 20 mg/m^2 every 4 weeks, and mitomycin C (MMC) at 2.7 mg/m^2 every 2 weeks were given to 42 patients. The remaining 14 patients received 5-FU at 330 mg/m^2 per week and epirubicin (EPIR) at 20 mg/m^2 every 2 weeks. As a rule, the treatment was performed on an outpatient basis. The side effects and complications observed included myelosuppression (41%), hepatic arterial occlusion (23%), and gastric mucositis (20%), but no major toxicity was encountered. The response rate (CR+PR) of the evaluated patients as determined from CT scans was 81%. The overall median survival period was 12.5 months. Only 14% of the patients died due to regrowth of liver metastases, and in 70% of the total cases, death due to liver metastases was avoided by this treatment. Thus, repeated hepatic arterial infusion chemotherapy for liver metastases from breast cancer might be capable of prolonging the survival of patients via avoidance of death due to the liver metastases.

Introduction

Liver metastasis is the poorest prognostic factor of recurrent breast cancer because (a) it is very rare for liver metastases from breast cancer to be resectable and (b) the effects of systemic chemotherapy and endocrine therapy on liver metastases are limited [12]. On the other hand, the techniques and equipment used for repeated hepatic arterial infusion chemotherapy have seen considerable progress in the last decade [2]. These techniques have shown good local control of liver metastases from colorectal and gastric cancers [3]. Therefore, if we could similarly control liver metastases from breast cancer by hepatic arterial infusion chemotherapy, it might be possible to prolong the patient's survival. The present study was carried out from this point of view.

Patients and methods

Between 1985 and 1992, 56 patients with liver metastases from breast cancer were entered in this study. For all of these patients, (1) the liver metastases were judged to be the limiting factor of survival based on the location and severity of the active lesions, (2) jaundice was not observed, (3) resection was not indicated, and (4) the performance status was grade 3 or lower according to the WHO criteria.

A catheter was inserted into the hepatic artery via the left subclavian artery and connected to a port implanted subcutaneously in the left subclavian space. In patients with multiple hepatic arteries, such as the left hepatic artery arising from the left gastric artery and the right hepatic artery arising from the superior mesenteric artery, all of the hepatic arteries except the one used for catheterization were embolized with steel coils. By this procedure, the one remaining patent hepatic artery supplied the blood flow to the entire liver through intrahepatic arterial anastomoses, and the infused drug thus reached the whole liver [4]. When necessary and feasible, arterial redistribution using steel coils was performed to prevent drug perfusion into the gastroduodenal artery and the right gastric artery. The patients' characteristics are summarized in Table 1.

The chemotherapy combination used in this study was FAM [5-fluorouracil (5-FU) + Adriamycin (ADR) + mitomycin C (MMC)] or FE [5-FU + epirubicin (EPIR)]. The details of the regimens were as follows. For 42 FAM patients, 330 mg/m^2 5-FU was given weekly, 20 mg/m^2 ADR was given every 4 weeks, and 2.7 mg/m^2 MMC was given every 2 weeks by bolus injection. For the remaining 14 FE patients, 330 mg/m^2 5-FU was given weekly and 20 mg/m^2 EPIR was given every 2 weeks. For each regimen, the administration was performed only when blood tests revealed a WBC count of $\geqq$2,000/mm^3 and a platelet count of $\geqq$50,000/mm^3 for 5-FU and a WBC count of $\geqq$3,000/mm^3 and a platelet count of $\geqq$100,000/mm^3 for ADR, MMC, and EPIR.

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Table 1. Patients' characteristics (n = 56)

Sex	All women
Age (years)	48.0±9.3 y
PS:	
0	7
1	21
2	19
3	9
Percentage of occupancy of the entire liver by the tumor:	
<30%	13
30%–60%	25
>60%	18
Extrahepatic lesions:	
(–)	9
(+)	47
Prior systemic/endocrine therapy:	
(–)	6
(+)	50

Table 2. Incidence of side effects and complications

Myelosuppression (≧ grade 3)	41%
Hepatic arterial occlusion	23%
Gastric toxicity (ulcer, gastritis, subjective symptoms)	20%

The treatments were continued for as long as possible. As a rule, systemic chemotherapy was not employed unless the liver metastases were well controlled and other systemic lesions became active. If necessary, locoregional treatments such as radiation therapy for bone metastases and intracavitary chemotherapy for peritoneal carcinomatosis were carried out. If the patient had previously received endocrine therapy, the same administration was continued. The response rate of liver metastases was evaluated by CT scans using standard ECOG response criteria, and the median survival was calculated by the Kaplan-Meier method.

Results

The number of administrations per patient ranged from 2–151 (mean, 31). The observed side effects and complications are shown in Table 2. Myelosuppression (≧ grade 3) was observed in 41% of the patients. Hepatic arterial occlusion occurred in 23% of the cases, and gastroduodenal toxicities – including endoscopically confirmed ulcers and gastritis and subjective symptoms such as nausea or epigastric discomfort – occurred in 20% of the cases. Myelosuppression was not very severe, and the blood parameters recovered to their normal ranges within 2–3 weeks in all cases. All side effects and complications could be managed by outpatient care, and no fatal toxicity was encountered. Most of the patients underwent this therapy on an outpatient basis except when in the terminal stage.

The response rate was evaluable in 53 patients, and the response rate was 81% (Table 3). The overall median survival period was 12.5 months. Significant differences in median survival were observed in relation to the existence of pleural or peritoneal carcinomatosis at the start of therapy and the response (Table 4). Of the 35 responder cases (CR + PR) who eventually died, only 14% died because of regrowth of liver metastases, whereas the remainder (86%) died due to other causes (Table 5).

Table 3. Response to treatment

CR	PR	NC	PD	NE	Response rate
10	33	6	4	3	81% (43/53)

Table 4. Median survival of patients

Overall	12.5 months (range, 3.0–64.0+ months)			
Pleural/peritoneal carcinomatosis:				
(–)	14.0 months	(+)	9.0 months	(P <0.05)
Response:				
(+)	16.0 months	(–)	5.0 months	(P <0.05)

Table 5. Causes of death in 35 responders

Pleural/peritoneal carcinomatosis	54%
Liver metastases	14%
Lung metastases	9%
Others	23%

Discussion

Liver metastasis is one of the patterns of systemic spread of breast cancer. Most breast cancer patients with liver metastases also have extrahepatic active lesions such as bone metastases, local recurrence, lymph node metastases, and peritoneal carcinomatosis. For the management of such patients, systemic chemotherapy is considered to be the standard therapeutic strategy [8]. However, the effects of systemic chemotherapy and endocrine therapy on liver metastases are limited, and liver metastasis is the poorest prognostic factor as compared with metastasis to other organs [12]. On the other hand, the survival period of patients who respond to systemic chemotherapy is longer than that of nonresponding patients [10]. Thus, good local control of liver metastases is required to prolong the survival of patients with liver metastasis from breast cancer.

From this point of view, repeated hepatic arterial infusion chemotherapy was employed for the treatment of these patients [1, 6, 7]. The techniques and equipment used for repeated hepatic arterial infusion chemotherapy have been established for the treatment of liver metastases from digestive organs such as colorectal and gastric cancers [3]. The advantages of this method employing percutaneous catheterization and an implantable port are that it can performed on an outpatient basis without invasion and it does not detract from the patient's quality of live.

The characteristics of the patients entered in this study indicate them to be standard for recurrent breast cancer with liver metastasis. Most of them had extrahepatic lesions and received prior systemic chemotherapy and/or endocrine therapy. The FAM regimen we used for 42 patients in this study has been widely used in Japan for hepatic arterial infusion chemotherapy for liver metastases from gastric cancer, and it showed a high response rate of 73% without producing any major toxicity. On the other hand, the FE regimen was applied to 14 patients to avoid the myelo-

suppression caused by MMC and the nausea induced by bolus injection of 20 mg/m^2 ADR. At present, the differences in side effects and responses between the FAM and FE regimens are unclear because the quantity of patients in the FE group was too small. However, on the basis of our clinical experience, we think that the results of both regimens are very similar.

The side effects and complications of this therapy were limited. Myelosuppression was observed in 41% of the cases but could be managed on an outpatient care basis. Hepatic arterial occlusion occurred in 23% of the cases and might have been related to the method of catheter insertion, because a high incidence of hepatic arterial thrombosis has been reported following catheter placement by the percutaneous approach [14]. The gastroduodenal toxicity observed in earlier cases in this study might have been caused by drug perfusion into the right gastric artery. However, we currently perform right gastric arterial embolization with small steel coils in most cases, and we apply the newly developed technique of arterial redistribution to avoid hepatic arterial thrombosis [2]. If these technical problems are excluded, the toxicities accompanying this therapy were very mild. Thus, at least from the viewpoint of toxicity, there is no reason for a patient to refuse hepatic arterial infusion chemotherapy as compared with systemic chemotherapy for the treatment of liver metastases from breast cancer.

Concerning the response of the liver metastases, the range of the response rates obtained with systemic chemotherapy was reported to be 20%–70%, and the average response rate was about 40% [5, 9, 11, 13, 15, 16]. Thus, the response rate achieved with hepatic arterial infusion chemotherapy was higher than those obtained with systemic chemotherapy. On the other hand, the overall median survival of our patients was not very long, being only 12.5 months. Our data showed the importance to survival of the presence of pleural/peritoneal carcinomatosis and the response to the therapy. However, concerning the causes of death in the 35 patients who responded, only 14% of them died due to regrowth of liver metastases. This means that we could control the liver metastases in the remaining patients who responded. They represented 70% of the total cases. In these cases, we could avoid death due to liver metastases by repeated hepatic arterial infusion chemotherapy, but some of these patients died due to progression of their extrahepatic lesions. Accordingly, this therapy might exert a positive effect on the survival of such patients.

Therefore, we conclude that repeated hepatic arterial infusion chemotherapy has much potential for preventing death due to liver metastases, and it might be capable of prolonging the patient's survival.

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