Cancer Chemother Pharmacol (1992) 31 (Suppl I): S99–S102

Cancer Chemotherapy and Pharmacology

Management of patients with unresectable liver metastases from colorectal and gastric cancer employing an implantable port system

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Summary. Between 1985 and 1990, 50 patients with unresectable liver metastases from colorectal cancer and 34 subjects with metastases from gastric cancer were treated by repeated hepatic arterial infusion chemotherapy employing an implantable prot system. A catheter was inserted into the hepatic artery via the left subclavian artery and was connected to the implantable injection port in each patient. 5-Fluorouracil (5-FU) at 330 mg/m^2 per week (167 mg/m^2 daily given continuously over the initial 3 months for colorectal cancer), 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 all 34 patients with gastric cancer and to 31 of the colorectal cancer patients. The remaining 19 patients with colorectal cancer received 5-FU at 1,000 mg/m^2 every week. As a rule the treatment was performed on an outpatient basis. The side effects and complications observed included myelosuppression (23%), hepatic arterial occlusion (21%), and gastroduodenal mucositis (12%), although no major toxicity was encountered. The response rate (CR+PR) among the evaluated patients as determined using CT scans was 67% for colorectal cancer and 73% for gastric cancer. The overall median survival was 12 months and 15 months, respectively. Good local control of liver metastases from the colorectal and gastric cancers was achieved by repeated hepatic arterial infusion chemotherapy employing an implantable port system without the need for hospitalization and without producing major toxicity. Thus, the implantable port system is very useful for the management of patients with unresectable liver metastases.

Introduction

Hepatic arterial infusion chemotherapy is one of the effective treatments for liver malignancies, especially hypovascular metastatic tumors for which transcatheter arterial chemoembolization (TAE) is not effective. However, as hepatic arterial infusion without an indwelling catheter requires hospitalization, repeated administration is not very practical. On the other hand, percutaneous hepatic arterial catheter placement has become easy due to recent advances in the technique for vascular interventional radiology. The combination of an indwelling hepatic arterial catheter and an implantable injection port has been widely used, and this combination makes repeated hepatic arterial infusion therapy possible on an outpatient bases [1, 6, 8]. This report describes the results we obtained using this system for hepatic arterial infusion chemotherapy of liver metastases from colorectal and gastric cancers.

Patients and methods

Between 1985 and 1990, 84 patients with liver metastases (50 from colorectal cancer and 34 from gastric cancer) were entered in this study. In all patients, (1) liver metastases were judged as the limiting factor of survival according to the location and severity of active lesions, (2) jaundice was not observed, and (3) the performance status was grade 3 or lower according to WHO criteria.

The catheter was inserted into the hepatic artery via the left subclavian artery and was connected to the port implanted in the subcutaneous space of the left chest wall. 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 hepatic arteries except the one used for catheterization were embolized by steel coils. By this procedure, the remaining hepatic artery supplied blood flow to the entire liver through intrahepatic arterial anastomoses and the infused drug thus reached the whole liver. 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 FA(E)M: 5-fluorouracil (5-FU) + Adriamycin (ADR) or epirubicin (EPIR) + mitomycin C (MMC). The details of the regimen were as follows. For 31 patients with colorectal cancer, 5-FU 165 mg/m^2 5-FU was given

* Presented at the Second International Symposium on Treatment of Liver Cancer. Taipei, 3–4 February 1991

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Table 1. Patients' characteristics

	Metastasis	
	Colorectal ($n = 50$)	Gastric ($n = 34$)
Sex (M/F):		
M	34	23
F	16	11
Age (years)	59.4±15.2	64.5±9.8
PS:		
0	7	5
1	27	15
2	12	9
3	4	4
Onset:		
Synchronous	35	14
Metachronous	15	20
Extrahepatic lesions:		
(–)	23	19
(+)	27	15
Percentage of occupancy of the entire liver by the tumor:		
<30%	11	11
30–60%	30	17
>60%	9	6
Histology:		
Well differentiated	10	1
Moderately differentiated	31	26
Poorly differentiated	1	2
P. med.		3
Mucinous	1	
Unknown	7	2

P. med., Poorly differentiated medullary type adenocarcinoma

Table 2. Incidence of side effects and complications

	Metastasis	
	Colorectal	Gastric
Myelosuppression (WBC, <2,000/mm³; platelets, <50,000/mm³)	18%	32%
Hepatic arterial occlusion	32%	6%
Gastroduodenal mucositis	20%	–
Nausea (>grade 2)	38%	35%

daily by continuous infusion for the initial 3 months, after which 330 mg/m² was given weekly by bolus injection. In addition, 30 mg/m² ADR was given every 4 weeks and 2.7 mg/m² MMC was given every 2 weeks, both by bolus injection. For the remaining 19 patients with colorectal cancer, 1,000 mg/m² 5-FU was given once weekly in a 5-h continuous infusion [3, 5]. For all 34 patients with gastric cancer, weekly doses of 330 mg/m² 5-FU, monthly doses of 20 mg/m² ADR or 30 mg/m² EPIR, and biweekly doses of 2.7 mg/m² MMC were given by bolus injection.

For each regimen, the administration was performed only when blood tests revealed a WBC of ≧2,000/mm³ and a platelet count of ≧50,000/mm³ for 5-FU and a WBC of ≧3,000/mm³ and a platelets count of ≧100,000/mm³ for ADR, EPIR, and MMC. The treatments were continued for as long as possible. The response of liver metastases was evaluated by CT scans using standard ECOG response criteria [18], and the median survival was calculated by the Kaplan-Meier method.

Table 3. Response to treatment

	CR	PR	NC	PD	NE	Response rate	
Colorectal	2	28	13	2	5	67% (30/45 patients)	
Gastric	4	18	7	1	4	73% (22/30 patients)	
Histology (colorectal):							
Well differentiated						100%	$P < 0.05$
Moderately differentiated						71%	
Histology (gastric):							
P. med.						0	$P < 0.05$
Others						89%	
Percentage of occupancy of the entire liver by the tumor:							
<60%						90%	$P < 0.05$
>60%						20%	

NE, Not evaluated; P. med., poorly differentiated medullary type adenocarcinoma

Results

The observed side effects and complications are shown in Table 2. Myelosuppression (≧ grade 3) was observed in 18% of the patients with colorectal cancer and in 32% of those with gastric cancer. Hepatic arterial occlusion occurred in 32% and 6% of cases; gastroduodenal mucositis, in 20% and 0; and nausea (grade 2), in 38% and 35% of the patients, respectively. 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 was evaluable in 45 patients with colorectal cancer and in 30 subjects with gastric cancer, and the response rates (CR+PR) were 67% and 73%, respectively. Significant differences in the response rate were observed in relation to the histological type of both cancers and to the percentage of occupancy of the entire liver by the tumor in the gastric cancer patients (Table 3). The overall median survival was 12 months in patients with colorectal cancer and 15 months in those with gastric cancer. Significant differences in median survival were observed in relation to the existence of extrahepatic lesions at the start of therapy of both cancers, the histological type of colorectal cancer, and the percentage of occupancy of the whole liver by the tumor in the gastric cancer patients (Table 4).

Discussion

There is no standardized chemotherapeutic regimen for the treatment of patients with advanced colorectal or gastric cancer, especially those with liver metastases. In patients with gastric cancer, many kinds of combination chemotherapy using 5-FU, ADR, MMC, and cisplatin (CDDP) have been given systemically, and the response rates have been 17%–65% [13, 14, 16, 17, 22, 23]. Recently, higher response rates of 43%–72% were reported for the EAP

Table 4. Median survival of patients

Colorectal:		
Overall	12 months	
Histology:		
Well differentiated	17 months	$P<0.05$
moderately	9 months	
Extrahepatic lesions:		
(–)	24 months	$P<0.05$
(+)	9 months	
Gastric:		
Overall	15 months	
Percentage of occupancy of the entire liver by the tumor:		
<60%	17 months	$P<0.05$
>60%	5 months	
Extrahepatic lesins:		
(–)	17 months	$P<0.05$
(+)	8 months	

combination (etoposide, ADR, and CDDP), but severe myelosuppression was also observed [10, 12, 19, 21]. In contrast, our hepatic arterial infusion chemotherapy using low-dose FA(E)M [2] yielded a high response rate of 73% without producing severe toxicity. As a result, this therapy could be performed on an outpatient basis without resulting in a disturbance of the patients' normal life-style.

When there is no possibility of prolonging the survival period, the influence of a chemotherapeutic regimen on the quality of life (QOL) is one of the most important factors in the selection of treatment. From this point of view, repeated hepatic arterial infusion using low-dose FA(E)M is a useful therapy because of its limited toxicity. Of course, in spite of the high response rate, the impact of this therapy on survival is uncertain, and randomized studies comparing i.v. and i.a. therapies for the treatment of liver metastases from gastric cancer are lacking. However, our data demonstrate a relatively long median survival of 17 months for patients who do not have extrahepatic lesions. A randomized study of i.v. versus i.a. therapy is now being conducted to reveal the impact of i.a. therapy on survival.

Many studies have been conducted on hepatic arterial infusion therapy for colorectal cancer using 5-fluorodeoxyuridine (FUDR) or 5-FU, and some randomized trials of i.v. versus i.a. therapy have been carried out in patients with this disease [7, 9, 11, 15]. In these studies, the response rate obtained using hepatic arterial infusion was approximately 50%, but in spite of this high response rate, no prolongation of the survival period was seen. The response rate of 67% obtained int the present study was almost the same as that obtained in previous trials. On the other hand, the toxicities encountered in our study were quite different from those reported for FUDR infusion. Hepatobiliary toxicities such as chemical hepatitis and sclerosing cholangitis were most frequently seen following FUDR infusion but were not observed in our patients.

The hepatic arterial occlusion observed in the present study might have been related to the method of catheter insertion. We inserted the catheter by the percutaneous approach in all cases, and a high incidence of hepatic arterial thrombosis following catheter placement by the percutaneous approach has been reported [20]. In the first half of our series of patients with colorectal cancer, the right gastric artery was open. This probably caused the occurrence of gastric ulcers or gastritis in these patients. 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 [4]. If these technical problems are excluded, the toxicities accompanying our therapy were very mild. In addition, the administration of 1,000 mg/m^2 5-FU by 5-h continuous infusion on a weekly schedule does not require an ambulatory or implantable continuous infusion system. Low toxicity and the use of a simple system are very important to the continuation of treatment over a long period. A larger study of this regimen is under way, and a randomized study of this hepatic arterial infusion therapy versus systemic therapy is being planned.

For both gastric cancer and colorectal cancer, hepatic arterial infusion therapy does not provide any remarkable survival benefit, but this therapy can achieve similar, if not better, response rates in liver metastases as compared with systemic treatment without producing major toxicity or an adverse effect on the patients' QOL. Repeated hepatic arterial infusion can be done only be employing an implantable port system. Therefore, this system is very useful for the management of patients with unresectable liver metastases.

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