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ORIGINAL ARTICLE

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Intermittent hepatic arterial infusion of high-dose 5FU on a weekly schedule for liver metastases from colorectal cancer

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Abstract *Purpose*: We performed phase I and II studies to examine the usefulness of intermittent hepatic arterial infusion of high-dose 5-fluorouracid (5-FU) for patients with liver metastasis from colorectal cancer. *Methods*: As the phase I study, 1000, 1250 and 1500 mg/m^2 of 5-FU were administered over 5 h by hepatic arterial infusion on a weekly schedule to establish the recommended dose. Based on the results of the phase I study, the phase II study was performed to confirm the efficacy of the recommended dose thus obtained. *Results*: In the phase I study, the dose-limiting factors of this therapy were gastrointestinal and central nervous system toxicities, and the recommended dose was judged to be 1000 mg/m^2. In the phase II study, 1000 mg/m^2 of 5-FU was administered over 5 h once a week on an outpatient basis, and this therapy was repeated as long as possible. The response rate was 78% (25/32), with an overall median survival time of 25.8 months (without extrahepatic lesions 25.9 months; with extrahepatic lesions 17.3 months). *Conclusions:* (1) Compared with conventional continuous infusion, the advantages of this therapy were that it caused no decrease in the patient's quality of life as a result of being permanently equipped with a pump and it thus enabled more cost-effective use of the pump, (2) The phase II study on 32 patients showed that this therapy caused no serious toxicities, with a response rate of 78% and a survival time of 25.8 months, which exceeded the results with conventional continuous infusion. If the reproducibility of these results is established in further studies involving multicenter collaboration, this therapy will be able to become the standard local chemotherapy for liver metastases from colorectal cancer. (3) Important problems remaining to be solved are improvement of the technical aspects and studies of combined use with systemic chemotherapy. Furthermore, to finally determine the position of this therapy in the treatment system for liver metastasis from colorectal cancer, it is necessary to conduct comparative trials versus systemic chemotherapy, using the survival time as the end-point.

Key words Hepatic arterial infusion · 5-FU · Liver metastasis · Colorectal cancer

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Introduction

Liver metastasis is the most common mode of metastatic recurrence of colorectal cancer and is the prognosis-determining factor in many cases, but its response to systemic chemotherapy is often poor. Hepatic arterial infusion as local chemotherapy has, therefore, been the routine treatment for unresectable cases. However, liver metastases from colorectal cancer respond poorly to bolus infusion, unlike metastatic lesions from gastric or breast cancer [7, 16, 21, 22]. Thus, it has been common to perform continuous arterial infusion of 5-fluorouracil (5-FU) in Japan and 5-fluorodeoxyuridine (FUDR) in Europe and the USA [6, 19, 23, 26]. This continuous infusion has achieved a high response rate of about 60%, which is an excellent result for chemotherapy of colorectal cancer. However, the use of a continuous infusion pump markedly decreases the quality of life (QOL) of the patients, and various problems associated therewith make it difficult to continue the therapy as long as needed. Because of this background, there has been a strong desire for a regimen attaining a high response rate of liver metastasis from colorectal cancer and not requiring patients to be permanently equipped with a continuous infusion pump. This desire led to the development of the present intermittent hepatic arterial infusion of high-dose 5-FU. In this report, we describe in detail how this therapy was developed and also discuss

Table 1 Conditions to be satisfied by the new hepatic arterial infusion chemotherapy

1. No need permanently to equip patients with a continuous infusion pump
2. Able to be repeated/continued for a sufficient period of time on an outpatient basis
3. Expectation of a response rate of 60% or higher

the results obtained in phase I and phase II clinical studies and the problems remaining to be solved.

Background of development

The conditions to be satisfied by the new therapy were as follows (Table 1):

1. Patients should not be permanently equipped with a continuous infusion pump. The greatest problem of conventional 5-FU continuous infusion chemotherapy, as described above, is that long-term use of the pump markedly decreases the patient's QOL and also makes long-term therapy difficult. To solve this problem, we considered it most important to improve the dosage schedule in order to make it unnecessary to permanently equip the patient with a continuous infusion pump.
2. The treatment should be able to be done on an outpatient basis. Many patients with liver metastases from colorectal cancer usually maintain a relatively good performance status except in their terminal stage, and this outpatient basis condition is thus considered very beneficial in order to continue the therapy for a long period of time in patients who have returned to normal life.
3. A response rate of 60% or higher could be expected. The new therapy would not be useful if it had decreased efficacy, however convenient it might be. We considered it necessary that the new method be able to achieve a therapeutic effect equal to or better than that of conventional continuous infusion. Although previously reported responses to continuous infusion chemotherapy vary somewhat, we set our goal at a 60% response rate as a result of reviewing various reports, including our own [6].
4. Several pilot studies have been performed to find a new therapy which satisfied these three conditions. From the results obtained, we judged administration of high-dose 5-FU over several hours to be promising. Assuming the continuous infusion time used in outpatient care to be 5 h, we performed a phase I study with the aim of determining the 5-FU dose which could be administered within this length of time.

Phase studies

Phase I study

This study is described in detail in references 9 and 13. The starting dose of 5-FU was fixed at 1000 mg/m^2 on a weekly schedule, and escalation in increments of 250 mg/m^2 was conducted while monitoring the toxicity. The subjects enrolled in this study were patients with unresectable liver metastasis from colorectal cancer who had a performance status of grade 0 to 2 and who gave informed consent. Three or four patients were used to evaluate each dose. A total of ten patients were treated, and the maximum dose was 1500 mg/m^2. As shown in Table 2, doses of 1250 mg/m^2 or higher caused gastrointestinal symptoms such as nausea and vomiting, and central nervous system toxicity such as headache and vertigo. Six of the seven patients treated at these doses required dose reduction to 1000 mg/m^2. On the other hand, in all patients treated at 1000 mg/m^2, and in those after dose reduction to 1000 mg/m^2, the therapy was able to be continued for more than 30 weeks.

Regarding the therapeutic effect, seven of the nine patients with high carcinoembryonic antigen (CEA) levels showed a 70% or more decrease in CEA levels, and a response rate of 80% was obtained when CT scan findings were evaluated according to the WHO criteria (Table 3). These results of the phase I trial indicated that the dose-limiting factors of this therapy are gastrointestinal and central nervous system toxicities and that the recommended dose should be 1000 mg/m^2. Furthermore, this therapy may be able to match the

Table 2 Side effects and dose reduction (phase I study)

Patient no.	Starting 5-Fu dose (mg/m^2)	Side effects	Dose reduction (mg/m^2)
1	1000	γ GTP elevated	No
2	1000	γ GTP elevated	No
3	1000	Malaise	No
4	1250	γ GTP elevated, nausea	To 1000
5	1250	Nausea, headache	To 1000
6	1250	γ GTP elevated, nausea	To 1000
7	1250	γ GTP elevated, nausea, malaise	To 1000
8	1500	γ GTP elevated, nausea, headache, dizziness	To 1250
9	1500	γ GTP elevated	No
10	1500	γ GTP elevated, nausea, dizziness	To 1000

Table 3 Response (phase I study) as evaluated from CT scans (*PR* partial response, *NC* no change, *NC* (*R*+) response below 50%)

Patient no.	Starting 5-Fu dose (mg/m^2)	Response	Reduction in CEA (%)
1	1000	PR	94
2	1000	PR	79
3	1000	PR	84
4	1250	NC (R+)	80
5	1250	PR	82
6	1250	PR	95
7	1250	PR	63
8	1500	NC (R+)	35
9	1500	PR	Negative
10	1500	PR	79

response rate of 60% reported with conventional continuous infusion chemotherapy. Accordingly, we judged that proceeding to a phase II trial was warranted.

Phase II study

Based on the results of the phase I study, a phase II study of this regimen was carried out [14]. The eligibility criteria were as follows: (1) the liver metastases were unresectable; (2) the prognostic limiting factor was clinically judged to be liver metastasis; (3) parenchymal jaundice was absent; and (4) the performance status was grade 0 to 3.

A total of 32 patients who gave informed consent were registered, and their characteristics are shown in Table 4. A catheter was inserted into the hepatic artery via the subclavian artery [1, 4, 5], and the proximal end of the catheter was connected to an implanted port system. On an outpatient basis, as a rule, 1000 mg/m^2 5-FU was administered over 5 h once per week, and this therapy was repeated as long as possible. In all patients, the right gastric artery was occluded with steel coils or ligated [2, 8, 15]. Great care was taken to prevent or quickly detect any disorders resulting from technical factors such as dislocation of the catheter, vascular occlusion or inadequate distribution of the drug, and if necessary, an adequate countermeasure was taken [10, 17].

As long as the arterial infusion was able to be continued, no other chemotherapies were used in combination. The median duration of the treatment was 10.9 months (3.3 to 29.1 months). The response was evaluated on the basis of the WHO criteria using CT scans. The results are presented in Tables 5 to 7. The side effects and complications observed are summarized in Table 5, but none was serious. The data on the response

Table 4 Patient characteristics (phase II study)

Characteristic	No. of patients
Sex	
Male	24
Female	8
Age (years)	60.8 ± 9.1
Performance status	
0	12
1	8
2	6
3	6
Onset	
Synchronous	25
Metachronous	7
Extrahepatic lesions	
No	21
Yes	11
Liver involvement (%)	
<30	11
30–60	16
>60	5
Histology	
Well	6
Moderate	24
Unknown	2

Table 5 Side effects and complications (phase II study)

Side effect or complication	Incidence
Nausea	
Grade 1	22% (7/32)
Grade 2	9% (3/32)
Dizziness	3% (1/32)
γ GTP elevation	13% (4/32)
Bile lake	13% (4/32)
Hepatic arterial occlusion	25% (8/32)

Table 6 Response (phase II study). Duration of responses: complete response, mean 14.7 months, range 6.0–85.9 months; partial response, mean 9.6 months, range 4.2–20.0 months

Complete response	Partial response	No change	Progressive disease	Response rate
4	21	6	1	78% (25/32)

Table 7 Survival (phase II study)

	Survival (months)
Overall	25.8 (6.5–89.2)
Patients without extrahepatic lesions	25.9
Patients with extrahepatic lesions	17.3

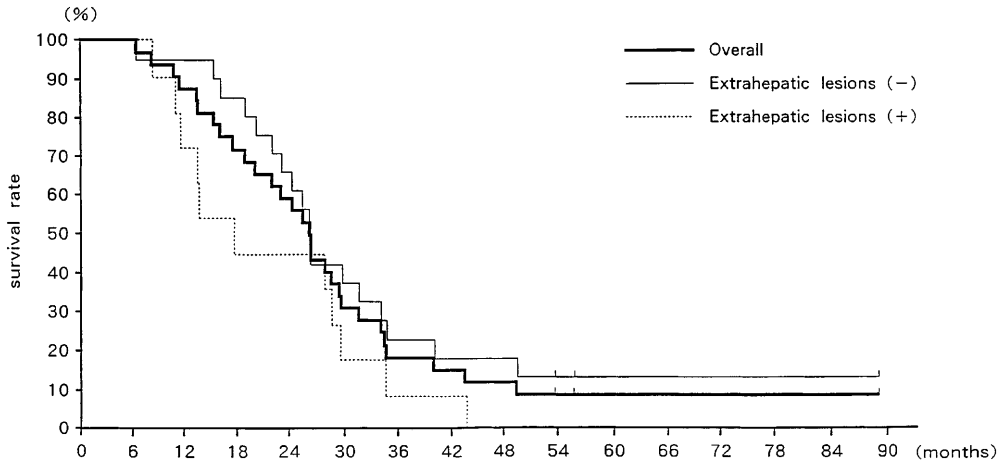

Fig. 1 The overall median survival time between patients without extrahepatic lesions and initial extrahepatic lesions

are shown in Table 6; the response rate was 78%. The overall median survival time, calculated by the Kaplan-Meier method, was 25.8 months (Fig. 1). When the relationship between the background factors and the median survival was examined, the survival time was significantly different between the patients without extrahepatic lesions on the diagnostic image at the time of starting the treatment (25.9 months) and those having initial extrahepatic lesions (17.3 months; Table 7).

Discussion

The toxicity of this therapy, including side effects and complications, was not markedly more severe than that of conventional continuous infusion [19], and the response rate in the phase II study was 78%, which is a very satisfactory result. The results of the phase I and II studies indicate that the aim of this therapy was achieved in making long-term use of a continuous infusion pump unnecessary, thereby improving the patient's QOL. Although this therapy also required the use of a continuous infusion pump during the 5-h administration period, it was unnecessary to permanently equip the patient with the pump, which permitted the use of one unit for multiple patients. This therapy was thus highly rated not only in relation to QOL but also to its cost-effectiveness, considering that continuous infusion pumps are still very expensive.

On the other hand, a problem remaining to be solved is the need to confirm the reproducibility of the results, because this study was small in scale, treating only 32 patients at a single institution. This point will be evaluated by additional multicenter collaborative studies. If the present results are reproducible in such additional studies, this therapy will be able to replace the conventional continuous infusion as the standard local chemotherapy for liver metastasis from colorectal cancer because of its convenience and effectiveness.

Not limited to this therapy and colorectal cancer, the most important question in arterial infusion chemotherapy for metastatic liver cancer is whether or not such local chemotherapy is practical and effective in prolonging survival, which is the primary purpose of cancer treatment [11]. Continuous infusion of FUDR has already been evaluated by randomized comparative trials versus systemic administration in the latter half of the 1980s in the USA, with negative results [18, 20, 24, 25]. On the contrary, another report has claimed that FUDR contributes to prolongation of survival if the FUDR dose is adjusted according to toxicity so that the therapy can be continued for a longer time [27]. Another study has shown a significant difference between continuous FUDR infusion and systemic FUDR [28]. At the present time, however, the negative view is dominant.

Because the final goal of cancer treatment is prolongation of survival, adequate evaluation of the therapeutic utility of this therapy requires establishment of its impact on this goal in randomized comparative trials versus systemic administration, with survival time as the end-point. The present study also showed that the presence of extrahepatic lesions significantly influences the survival time. It is, therefore, of great importance to investigate the combined use of arterial infusion chemotherapy and systemic administration with the aim of inhibiting the occurrence or aggravation of extrahepatic lesions. The steps to be followed for efficiently examining these problems are:

1. confirmation of the reproducibility of the efficacy of this therapy by a multicenter collaborative study;
2. investigation of the control of extrahepatic lesions by combination of this therapy and systemic chemotherapy; and
3. evaluation of hepatic arterial infusion chemotherapy by a randomized comparative trial versus systemic chemotherapy, with survival time as the end-point.

It is the authors' view that the most important factor influencing the ability of hepatic arterial infusion therapy to improve survival time is how long the therapy can be continued. Therefore, it is also essential to improve the technical aspects of hepatic arterial infusion during the course of the above studies [3, 12]. Although, solving

these problems undoubtedly entails many difficulties, such investigations are indispensable to the establishment of the significance of arterial infusion chemotherapy for liver metastases from colorectal cancer.

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