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Low-dose Leucovorin and 5-Fluorouracil for Unresectable Multiple Liver Metastasis from Colorectal Cancer

KEIICHIRO ISHIBASHI*, KAZUHIKO YOSHIMATSU*, HAJIME YOKOMIZO, ARIHIRO UMEHARA, KIYOHITO YOSHIDA, TAKASHI FUJIMOTO, KIYO WATANABE, TAKAO KATSUBE, YOSHIHIKO NARITAKA and KENJI OGAWA

Department of Surgery, Tokyo Women's Medical University Daini Hospital, 2-1-10 Nishiogu, Arakawa-ku, Tokyo, 116-8567, Japan

Abstract. *In the present study, a retrospective investigation was conducted to determine whether or not it was possible to obtain a comparable survival time, response rate (RR) and modest toxicity combining low-dose leucovorin (LV) and 5-Fluorouracil (5-FU) (LV/5-FU) with hepatic arterial infusion (HAI) or systemic intravenous infusion (SI) for patients with unresectable liver metastasis from colorectal cancer (CRC). Patients and Methods: Patients were given LV at 20 mg/m^2 immediately followed by 5-FU at 370 mg/m^2 with a 2-hour SI or HAI daily for 5 consecutive days with courses repeated every 5 weeks. Twenty patients received HAI and 16 patients received SI. Survival, response and toxicity were assessed. Results: The median survival time (MST) of all patients was 20.0 months. The MST of the HAI and SI patients was 24.5 and 18.9 months, respectively. Two patients had complete remission (CR), 8 partial response (PR) and 14 no change (NC), which resulted in an RR of 28%. The MST according to the responses of CR/PR, NC and progressive disease (PD) patients was 45.5, 20.2 and 11.2 months, respectively. Severe toxicity (grades 3 or 4) to this regimen occured only in 0-10% of the cases, and there were no treatment-related deaths. Conclusion: There was no difference in response and survival between HAI and SI, which could be interpreted as a favorable result. Regardless of the route of administration, low-dose LV/5-FU treatment should be considered for patients with liver metastasis from CRC.*

Metastatic and advanced colorectal cancer (CRC) is one of the more chemotherapy-resistant solid tumors. Since the late 1950's, 5-Fluorouracil (5-FU) had been the key drug, but the response rate of single administration was only 10-20%, and the median overall survival did not exceed 1 year, thus, providing no evidence that such treatment improves patients' survival (1, 2).

Randomized clinical trials have investigated the efficacy of single-agent 5-FU *versus* 5-FU with leucovorin (LV) (LV/5-FU) using several different regimens (3-8). Significantly higher response rates and prolonged survival have been reported with 5-FU/LV regimens (3-7).

With metastatic CRC, in particular, most of the tumors may be located in the liver (9-11). Hepatic resection is the best treatment when the hepatic metastases are isolated, but this is only feasible in 20-50% of the cases and for these patients the 5-year survival rate is 20-50% (12-15). Control of hepatic metastases is important for prognosis. When metastases are unresectable but confined to the liver, hepatic arterial infusion (HAI) can be a valid therapeutic option. Several studies have shown, comparing HAI and systemic intravenous infusion (SI), that HAI was able to increase the response rate, however, HAI did not contribute to the survival rate (16-23).

The combination of 5-FU and LV has been extensively studied using different doses of the 2 drugs (3-5, 8, 24-33). However, there is still controversy concerning the optimal dosages and administration schedules.

In the present study, we retrospectively investigated whether or not it would be possible to obtain a comparable survival time, response rate (RR) and modest toxicity by combining 5-FU and low-dose LV for a type of modified Mayo regimen infused intravenously (3, 4, 24, 25) or through the hepatic artery route.

*These authors contributed equally to this work.

Abbreviations: LV, leucovorin; 5-FU, 5-Fluorouracil; CRC, colorectal cancer; PS, performance status; MST, median survival time; CR, complete remission; PR, partial response; NC, no change; PD, progressive disease; RR, response rate.

Correspondence to: Kenji Ogawa, Department of Surgery, Tokyo Women's Medical University Daini Hospital, 2-1-10 Nishiogu, Arakawa-ku, Tokyo, 116-8567, Japan. Tel: +81-3-3810-1111, Fax: +81-3-5855-7276, e-mail: ogawasu@dnh.twmu.ac.jp

Key Words: Colorectal cancer, liver metastasis, leucovorin, 5-Fluorouracil.

Patients and Methods

Patients. Thirty-six patients with unresectable multiple liver metastasis, who had been admitted to our hospital from 1995 to 2002 and who had a histological presentation of colorectal adenocarcinoma with a complete curative resection of the primary tumor and synchronous or metachronous unresectable multiple liver metastasis, were enrolled in the study. Patients whose extrahepatic metastases were not detected at the time of the diagnosis of liver metastasis were not eligible. All the patients had diseases that could be evaluated, and their performance status (PS) was less than an Eastern Cooperative Oncology Group (ECOG) PS of 2. Adequate hematological function (total leukocyte count >3,000/ml and platelet count >80,000/ml), renal function (serum creatinine <1.5 mg/ml) and hepatobiliary function (total serum bilirubin <1.5 mg/ml) were also essential. Informed consent was obtained from all patients before beginning the treatment.

Chemotherapy regimen and treatment method. Patients were given LV at 20 mg/m^2 immediately followed by 5-FU at 370 mg/m^2 as a 2-hour SI or HAI, daily for 5 consecutive days every 5 weeks. All patients had to have an intra-arterial catheter inserted for HAI. A totally implantable silicone arterial catheter (Horizon Medical Products, Manchester, GA, USA) was inserted intra-operatively, during the resection of the primary tumor. The catheter was either inserted percutaneously from the right gastroepiploic artery with the tip remaining in a gastroduodenal artery, or was inserted into a subclavian or femoral artery with interventional radiology with the tip remaining in a common hepatic artery, thereby gaining access to the hepatic arterial flow. The other end was connected to a subcutaneous infusion port (34-36). Operative or interventional arterial redistribution was performed for vessels other than the hepatic artery and, whenever possible, a cholecystectomy was routinely performed to prevent drug-induced cholecystitis. If intra-arterial catheter implantation was impossible because of technical difficulties or previously unrecognized arterial abnormalities, then those cases were moved to the SI group. To avoid vomiting, granisetron was administered (37). When toxicities were noted, administrations were delayed or the dose was reduced. If progressive disease was detected in an evaluation, patients were given the option of switching to best supportive care or second-line chemotherapy, *e.g.*, the CPT-11 and CDDP regime (CPT-11 and CDDP were administered on days 1, 8 and 15 every 4 weeks as one cycle. CPT-11 at 27 mg/m^2 was dissolved in 500 ml 5% glucose and infused intravenously over 120 min. Subsequently, CDDP at 6 mg/m^2 was dissolved in 100 ml saline and infused for 30 min) (38).

Evaluation. The tumor response was evaluated based on changes in the size of measurable lesions as assessed by CT scans and ultrasonography. The assessment of tumor response and toxicities was classified in accordance with World Health Organization criteria (39). Briefly, complete remission (CR) was defined as the disappearance of all evidence of tumor for a minimum of 4 weeks. Partial response (PR) was defined as 50% or more reduction in the sum of the products of perpendicular diameters of all measurable lesions for a minimum of 4 weeks without any evidence of new lesions or enlargement. Progressive disease (PD) was defined as a greater than 25% enlargement of an existing lesion or the development of one or more new lesions. Lesions that did not meet the criteria for response or progression were classified as having no change (NC). The worst grade during the entire treatment was used for the evaluation of toxicities.

Table I. *Patient characteristics.*

Characteristics	n
Total number of patients	36
Median age, years (range)	62 (43-81)
Gender (M:F)	26:10
Performance status	
0-1	36
2-	0
Median cycles (range)	7 (2-18)
Timing of liver metastases	
synchronous	25
metachronous	11
Pretreatment	
5-FU alone	8
none	3
Treatment	
hepatic arterial infusion (HAI)	20
systemic infusion (SI)	16
Second-line chemotherapy	
CPT-11, CDDP	17
none	19

The survival times of this study were calculated after the initiation of 5-FU and low-dose LV using Kaplan-Meier's methods. The *p*-values for survival comparisons of treatment were obtained using log-rank analysis. The Pearson's χ^2 statistic was used for response comparisons. A *p*-value of >0.05 was considered significant. All calculations were performed using Stat View 5.0J software (Abacus Concepts. Inc, CA, USA).

Results

Patient characteristics. The patient characteristics are shown in Table I. The median age was 62 (43-81) and all patients were PS 0-1. The median cycles of this regimen were 7 (2-18). Regarding the timing of liver metastases, 25 patients were synchronous and 11 patients were metachronous, of which 8 patients received a 5-FU-based chemotherapy after resection of the primary tumor. Twenty patients received HAI and 16 patients received SI. When progressive disease was detected by evaluation, 17 patients were switched to a second-line chemotherapy (CPT-11 and CDDP regime) (38).

Patient survival. The survival curves for all patients are shown in Figure 1. The median survival time (MST) of all patients was 20.0 months. The MST of synchronous patients was 20.0 months and that of the metachronous patients was 20.2 months (Figure 2). The MST of HAI patients was 24.5 months and of SI patients was 18.9 months (Figure 3). There was no significant survival advantage compared with the timing of liver metastases and treatment.

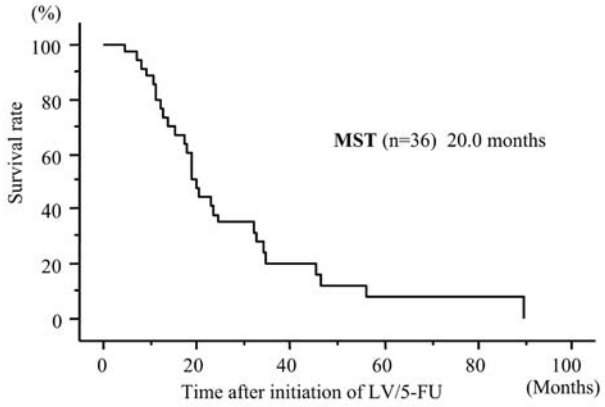

Figure 1. *Survival curve of all patients in this study: median survival time (MST) of all patients was 20.0 months.*

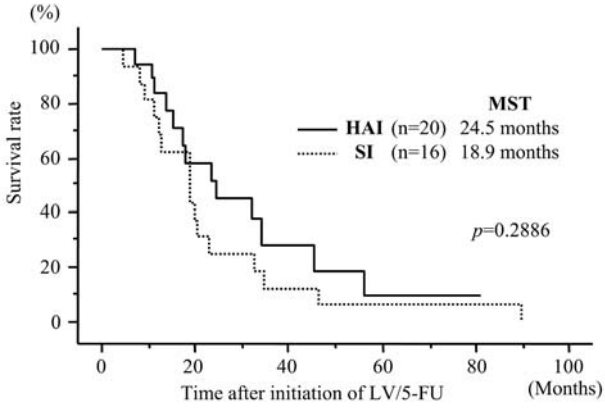

Figure 3. *Survival curve according to treatments: MST of HAI patients was 24.5 months, SI patients was 18.9 months.*

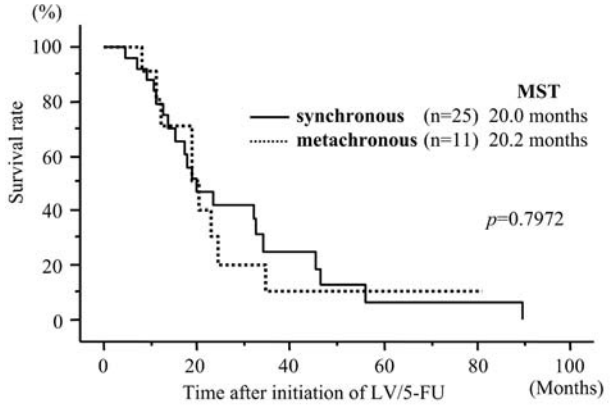

Figure 2. *Survival curve according to timing of liver metastases: MST of synchronous patients was 20.0 months, metachronous patients was 20.2 months.*

Table II. *Responses with treatment.*

	CR	PR	NC	PD	RR (%)	
Overall (n=36)	2	8	14	12	28	
Timing of liver metastases						
synchronous (n=25)	2	6	10	7	32	]
metachronous (n=11)	0	2	4	5	18	] n.s
Treatment						
HAI (n=20)	1	6	9	4	35	]
SI (n=16)	1	2	5	8	19	] n.s

Abbreviations: CR, complete remission; PR, partial response; NC, no change; PD, progressive disease; RR, response rate; HAI, hepatic arterial infusion; SI, systemic infusion.

Response. The responses among the 36 patients with treatment are provided in Table II. Two patients were evaluated as CR, 8 patients were PR, 14 patients were NC and 12 patients were PD, resulting in an RR of 28% (10 out of 36 patients). According to the responses, the MST was 45.5 months in the CR/PR patients (10 patients), while it was 20.2 and 11.2 months for the NC (14 patients) and PD patients (12 patients), respectively (Figure 4). There was no significant survival difference between CR/PR, NC and PD patients. As for the timing of liver metastases, in the synchronous patients, 2 patients were CR and 6 PR, with a RR of 32% (8 out of 25 patients), while in the metachronous patients, no patients were CR, 2 PR, with a RR of 18% (2 out of 11 patients). There was no significant difference in response between the timing of liver metastases. According to the treatment in the HAI patients, 1 patient was CR and 6 PR, giving a RR of 35% (7 out of 20 patients), while in the SI patients, 1 patient was CR and 2 PR, with a RR of 19% (3 out of 16 patients). There was no significant difference in response between treatments.

Toxicity. The toxicity to this regimen on HAI and SI are shown in Tables III and IV. Considering the worst level of toxicities occurring in each case, 30-50% of the patients experienced nausea, diarrhea, stomatitis and/or anorexia, but these were severe (grades 3 or 4) in only 0-10% of the cases, and there were no treatment-related deaths.

Discussion

Various studies have been carried out on advanced CRC that compared the dosage of LV, to determine whether it

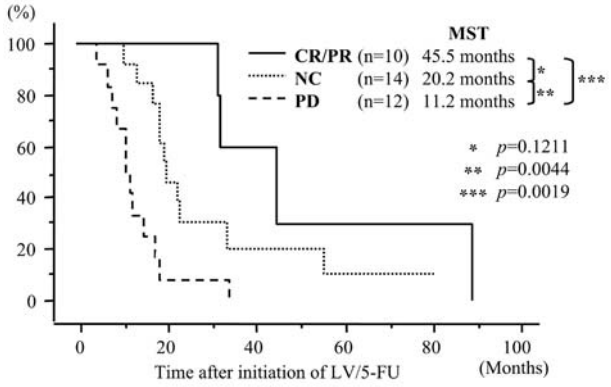

Figure 4. *Survival curve according to the responses: MST of CR/PR patients was 45.5 months, NC patients was 20.2 months and PD patients was 11.2 months.*

Table III. *Toxicity with HAI (hepatic arterial infusion) (n=20).*

	Grade				%	
	0	1	2	3-4	1-4	3-4
Leukopenia	16	0	2	2	20.0	10.0
Nausea	13	4	3	0	35.0	0
Diarrhea	13	4	1	2	35.0	10.0
Alopecia	18	1	1	0	10.0	0
Stomatitis	13	5	1	1	35.0	5.0
Anorexia	12	3	4	1	40.0	5.0

Table IV. *Toxicity with SI (systemic intravenous infusion) (n=16).*

	Grade				%	
0	1	2	3-4	1-4	3-4	
Leukopenia	13	1	1	1	18.8	6.3
Nausea	9	4	2	1	43.8	6.3
Diarrhea	12	1	3	0	25.0	0
Alopecia	15	0	1	0	6.3	0
Stomatitis	11	3	1	1	31.3	6.3
Anorexia	9	5	2	0	43.8	0

should be low or high, and whether in bolus or in continuous intravenous infusion (3-8, 24-34). According to the meta-analysis group (40), the MST in continuous patients was superior to that of bolus patients, at 22 months *vs.* 14 months, respectively. However, in these reports (3-8, 24-34), RRs were 10-40%, but MSTs were only 9-15 months, and the dosage and bolus format were not determined. In the present study, the results are limited to the effects of liver metastasis.

However, the occurrence of severe toxicity (grade 3 or 4) is less than the low rate of 10%, and these therapeutic effects result in approximately 20 months of MST, which can be considered as favorable. Considering the cause of these good results, the MST, according to the RR, for the PD patients was only 11.2 months, and was 20.2 months for NC patients and 45.5 months for CR/PR patients. It is as though NC patients received a gain in survival time without the usual, compulsory tumor shrinkage. For solid tumors including colorectal cancer, the efficiency of chemotherapy is low and, therefore, a physician cannot always expect a complete cure. To date, the primary objective of chemotherapy has been tumor shrinkage, however, the current thought is that tumor shrinkage is not necessarily a part of the treatment strategy. It is, therefore, necessary to rethink the idea that one of the principal concerns of the treatment strategy should be to clinically lengthen the dormant state, the period of no change.

The survival time of most patients with solid tumors depends on survival by an induced cytostatic effect rather than on tumor reduction (41). We believe that our results sufficiently illustrate that point. An effective decision regarding chemotherapy should be made in consideration of the RR and survival time. As an evaluation, RR is often more useful compared with survival time, because a survival time evaluation requires so much time in itself. However, the final goal of chemotherapy is increasing the time of survival, and not tumor shrinkage. For survival without tumor shrinkage, it is necessary to change our basic thinking regarding the kind, the amount, and the way and period of administering the medicine.

A comparative examination of HAI, mainly on fluorodeoxyuridine (FUDR) and SI, has been done, and a good response is reported in HAI (16-22). These studies reported that the RRs of HAI patients were 40-62%, however, that of the SI patients were 10-21%, while the MST for HAI patients was 12.6-17 months, whereas that of the SI patients was 10-21 months. HAI obtained a good RR but did not lengthen the survival time. In meta-analysis, the odds ratio of a tumor shrinkage effect in 0.25 (95% confidence section 0.16-0.40), concluded that HAI is meaningful, and an extension effect was recognized in survival time (42). In the present study, two routes of administration were investigated retrospectively with the same regimen. There was no significant survival benefit with HAI compared with SI, however, the MST with HAI was 24.5 months, significantly longer than that of those patients receiving the HAI treatment previously reported. Further examination is warranted to clarify whether or not HAI has an advantage in treating liver metastasis. However, some remaining problems, such as the catheter insertion technique and the unified arterial blood supply (43), must be resolved. In addition, infusionable LV/5-FU regimens, in combination

with CPT-11 or oxaliplatin have already been standardized for advanced CRC patients (44, 45). The benefits of these regimens administered through HAI should be determined in future studies.

Although a randomized control study must be performed to clarify these problems, we can conclude that, regardless of the administration route, low-dose LV/5-FU treatment should be considered for patients with liver metastasis from CRC.

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