Table IV. *Immunological and clinical responses.*

Pt.	No. of vacc.	Vacc. site reaction	CTL response (peptide-specific interferon-γ production by ELISPOT assay)							Clinical response	OS (days)
			RNF43	TOMM34	FOXM1	MELK	HJURP	VEGFR1	VEGFR2		
1	80	Ind, red	+	+	+++	+++	+	+++	+	PR	676 (alive)
2	24	Ind	+	–	+++	+++	+	+++	–	PD	198
3	64	Ind, red	+	+	+++	+++	+	+++	+	SD	490
4	8	None	NA	NA	NA	NA	NA	NA	NA	PD	130
5	65	Ind	+	+	+++	+++	+	+++	+	SD (OR)	551
6	64	Ind	+	+	+++	+	+	+	+	SD	575 (alive)
7	15	Ind	–	+	+++	+	–	+	+	SD (OR)	103
8	18	Ind	–	+	+++	+++	+	+	+	SD	122
9	62	Ind	+	+	+++	+++	–	+++	+	SD	554 (alive)
10	14	Ind, red	–	–	+++	+++	+	+	+	SD	158
11	13	Ind, red	–	–	+++	–	–	–	–	SD (OR)	209
12	20	Ind	+	+	+++	+++	–	+++	+	SD	215
13	26	Ind	–	–	+++	+++	+	+++	+	PR	324
14	9	None	+	–	+++	+	–	–	–	PD	70
15	58	Ind	–	–	+++	++	+	+++	+	SD	507
16	57	Ind	+	+	+++	+++	+	+	+	PR	533 (alive)
17	12	None	–	+	+++	–	–	+	–	PD	92
18	15	Ind, red	+	+	+++	+++	+	+	–	PD	159
19	17	Ind	–	+	+++	+++	–	+++	–	PD	134
20	8	None	+	–	–	–	NA	+	–	SD	70
21	55	Ind, red	+	+	+++	+++	+	+++	+	PD	498 (alive)
22	58	Ind	+	+	+++	+++	+	+++	+	SD	519 (alive)
23	13	Ind	+	+	+++	+++	–	+	+	PD	319
24	18	Ind, red	–	+	+++	+++	–	+++	–	SD	123
25	30	Ind	–	+	+++	+++	+	+++	+++	PD	307
26	6	None	+	+	+++	+	–	+	–	PD	91
27	23	Ind	–	+	+++	+++	–	+	+	PD	376
28	50	Ind, red	+	+	+++	+++	+	+++	+	SD	407 (alive)
29	27	Ind, red	+	–	+++	+++	+	+++	+	SD	279
30	38	Ind	+	+	+++	+++	+	+	++	PD	288 (alive)

Ind, induration; red, redness; CTL: cytotoxic T lymphocyte; CTL response (IFN-γ ELISPOT assay): CTL responses were classified into 4 grades (–, +, ++, and +++) depending on the amounts of peptide-specific spots, see text; PR, partial response; SD, stable disease; OR, objective response; PD, progressive disease; NA: not assessed; RNF43: ring finger protein 43; TOMM34: translocase of the outer mitochondrial membrane 34; FOXM1: forkhead box M1; MELK: maternal embryonic leucine zipper kinase; HJURP: holliday junction-recognizing protein; VEGFR: vascular endothelial growth factor receptor.

'key CTL responses' to the 7 peptides are the major contributors. Neither total white blood cell counts or peripheral blood lymphocyte counts before vaccination, nor ELISPOT peptide-specific IFN-γ production before vaccination by ELISPOT assay correlated with peptide-specific CTL responses (data not shown).

The advantages of multi-antigen vaccines have been discussed in the Food and Drug Administration Guidance, which raised the possibility that multi-antigen vaccines not only induce multiple tumor-specific immunological responses, but also hinder potential tumor-escape mechanisms (17). Moreover, Walter *et al.* demonstrated the multiple tumor-associated peptides composed of 11 peptides induced potent immune responses and resulted in long-term survival of patients with renal cancer in several clinical trials (IMA901) (18).

While the data presented in this report are promising for the treatment of mCRC using a multipeptide vaccine and UFT/LV, the therapeutic outcome achieved thus far is still not optimal. Potential reasons for the limited success in this trial include immune regulation mediated by cancer cells and leukocyte populations through a variety of cell-surface and secreted molecules, including regulatory T-cells, myeloid-derived suppressor cells, and activated (type 2) macrophages (M2).

Walter *et al.* reported that cyclophosphamide pretreatment before multipeptide vaccination successfully reduced the numbers of regulatory T-cells as determined by

immunophenotyping, and resulted in long-term survival of patients with advanced renal cell cancer in a randomized trial (18). Therefore, further clinical trials directed at the blockade of suppressive immune responses, including immune checkpoint antibodies such as to programmed death 1(PD-1)/programmed death ligand 1(PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), are attractive options for improving clinical responses in conjunction with this peptide vaccine and UFT/LV (19).

Finally, regorafenib is currently the only available treatment for recurrent CRC when standard chemotherapy has failed. Regorafenib is a novel oral multikinase inhibitor that blocks the activities of several protein kinases, including kinases involved in the regulation of tumor angiogenesis (VEGFR1, VEGFR2, VEGFR3, TIE2) and oncogenesis (KIT, RET, RAF1, BRAF and $BRAF^{V600E}$). In the recent multicenter, randomized, placebo-controlled CORRECT trial, the MST of the regorafenib group was reported to be 6.4 months, while the MST of the placebo group was 5.0 months (20). In comparison, the patients in our trial with almost the same background as that of the CORRECT trial had a MST of ~~10.8~~ months with peptide vaccination, although our trial was a preliminary pilot study for HLA-A24-positive patients and had a far smaller sample size. We are planning to undertake a randomized placebo-controlled multipeptide trial for HLA-A24-positive patients with mCRC refractory to standard chemotherapy to further explore this form of cancer vaccine.

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Conflicts of interest

The Authors declare no conflict of interest.

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Unresectable Colorectal Liver Metastases: The Safety and Efficacy of Conversion Therapy Using Hepatic Arterial Infusion Immunochemotherapy with 5-Fluorouracil and Polyethylene Glycol-Interferon α-2a

Takuya Nakai · Kiyotaka Okuno · Hiroshi Kitaguchi · Hajime Ishikawa · Mitsuo Yamasaki

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Abstract

Background Hepatic arterial infusion (HAI) or systemic chemotherapy has been used to treat unresectable colorectal liver metastases. The prognosis of the disease in recent years has been improved because chemotherapy is performed before hepatectomy to reduce tumor size (conversion therapy). The purpose of this study was to investigate the safety and efficacy of conversion therapy following HAI immunochemotherapy.

Methods Hepatic arterial infusion of 5-fluorouracil (5-FU)/polyethylene glycol (PEG)-IFNα-2a was performed in 21 patients. The primary endpoint was the safety of HAI and hepatectomy. The secondary endpoints were response rate, rate of conversion to hepatectomy, survival rate, and prognostic factors.

Results With regard to side effects, drugs were discontinued temporarily in one patient because of a decrease in white blood cell count; however, other patients continued chemotherapy. The response rate with HAI was 61.9 %, and the conversion rate was 38.1 %. Hepatectomy was completed successfully without mortality. Median progression-free survival (PFS) was 11.5 months (with and without conversion, 16.7 and 4.8 months, respectively; $p = 0.021$). Median overall survival was 34.6 months (with and without conversion, 48.4 and 26.6 months, respectively; $p = 0.003$). Prognosis was poor when the number of metastatic tumors was ≥10 [PFS: hazard ratio (HR) 32.21, $p = 0.003$; overall survival (OS): HR 9.13, $p = 0.07$], but prognosis improved after hepatectomy (OS: HR 0.08, $p = 0.09$).

Conclusions Hepatic arterial infusion immunochemotherapy with 5-FU/PEG-IFNα-2a was performed safely without major side effects. Prognosis is expected to improve after successful conversion to hepatectomy.

T. Nakai (✉) · K. Okuno · H. Kitaguchi · H. Ishikawa · M. Yamasaki
Department of Surgery, Faculty of Medicine, Kinki University, 377-2 Ohno-Higashi, Osaka-Sayama 589-8511, Osaka, Japan
e-mail: nakai@surg.med.kindai.ac.jp

Introduction

Approximately 20–30 % of patients with advanced colorectal cancer develop liver metastasis during the course of treatment. Therefore, management of liver metastases, together with lung and lymph nodes metastases, is an important issue in the treatment of colorectal cancer. In the case of resectable liver metastasis, hepatectomy is performed with a favorable 5-year survival rate of 30–50 % [1]; however, only 20 % of liver metastases are resectable [2].

Hepatic arterial infusion (HAI) chemotherapy has conventionally been performed as a regional treatment for unresectable liver metastases, using drugs with a high hepatic extraction ratio, such as floxuridine (FUDR) [3]. Compared with systemic chemotherapy, HAI has relatively mild adverse effects and enables a better quality of life [4]. Okuno et al. [5] focused on interleukin-2 (IL-2), a T cell growth factor, for use in the biochemical modulation (BCM) of 5-fluorouracil (5-FU) and performed a HAI immunochemotherapy using IL-2, 5-FU, and mitomycin C(MMC) in a phase II, prospective, randomized study. In the study, the response rate increased from 40 to 78 % with the addition of IL-2. Another study performed systemic administration of 5-FU and interferon α (IFNα) to treat advanced colorectal cancer, and a response rate of 76 % was obtained [6]. In HAI, 5-FU, folinic acid, IFNα-2b, and

degradable starch microspheres (DSM) have been used [7]. These results indicate that the use of HAI immunochemotherapy ensures safety and high treatment efficacy.

In recent years, hepatectomy has been performed in "conversion therapy" when systemic chemotherapy or arterial infusion successfully converts an unresectable liver metastasis into a resectable one by reducing its size, and this proactive surgical treatment obtained long-term survival [2]. We performed a phase I study of HAI immunochemotherapy with 5-FU and PEG-IFNα-2a followed by conversion therapy for unresectable colorectal liver metastasis. The primary endpoint of the study was the safety of HAI and hepatectomy during conversion therapy. The secondary endpoints were response rate, rate of conversion to hepatectomy, survival rate, and prognostic factors.

Patients and methods

All patients had unresectable liver metastases that were histologically defined as colorectal adenocarcinoma. Patients with extrahepatic metastasis were excluded from the study. Hepatic tumors are defined as unresectable if resection would result in remnant liver volume of ≤30 % of the original volume or a tumor involving all three main hepatic veins or both inflow pedicles. Inclusion criteria included no metastases to other organs, ≥60 % on the Karnofsky performance status scale, and age of 20–79 years. Clinical examination showed the following: a white blood cell count ≥1,500 cells/mm^3 and a platelet count ≥50,000 cells/μL as functional indicators of bone marrow; AST and ALT ≤ 100 IU/L and T-Bil ≤ 2 mg/dL as hepatic function indicators; and renal function with Cr ≤ 2 mg/dL. In patients who had been undergoing systemic chemotherapy with the use of, for example, 5FU/leucovorin/oxaliplatin or 5FU/leucovorin/irinotecan, before the present study, drugs were discontinued for at least 1 month. Written, informed consent was obtained, and this study was approved by the Ethics Committee of Kinki University School of Medicine (approval number, 19–36).

Catheter placement

Before therapy, a radiologist inserted a catheter (Anthron PU catheter, Toray Medical, Chiba, Japan) into the femoral artery [8, 9]. The catheter tip was inserted into the gastroduodenal artery by fixing with a metallic coil, and the side hole was positioned at the common hepatic artery. The right gastric artery and the accessory hepatic artery (e.g., the right hepatic artery from the superior mesenteric artery) was embolized using coils [9], and the proximal end of the catheter was connected to an implanted port (Selsite Port, Toray Medical) and embedded into the thigh.

Immunochemotherapy administration and follow-up

Using a syringe pump, arterial infusion of 500 mg/m^2 of 5-FU and 90 μg/body of PEG-IFNα-2a (Pegasys® Chugai pharmaceutical, Tokyo, Japan) in 20 ml of saline was performed once a week for 90 min, and one cycle consisted of four infusions. After every cycle, complete blood count, liver function, and carcinoembryonic antigen were measured. Adverse events were evaluated in accordance with Common Terminology Criteria for Adverse Events v 3.0 [10]. Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 [11] was used to assess the efficacy of therapy. Computed tomography (CT) was performed after three cycles. When CT revealed shrinkage of a metastatic tumor, and if 40 % of remnant liver volume was achievable, then the therapy was converted into hepatectomy. Radiofrequency ablation (RFA) was exclusively performed for multiple bilateral metastases in combination to hepatectomy. They were used for metastatic tumors ≤2 cm in size deep inside the liver. Before surgery, the indocyanine green 15-min retention rate (ICG R15) was estimated. Portal vein embolization (PVE) and two-stage hepatectomy were not performed. Systemic chemotherapy was started when RECIST indicated progressive disease (PD).

Statistical analysis

Patient characteristics were compared using Fisher's exact test. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan–Meier method. Survival curves were compared using the log-rank test. A p value <0.05 was considered significant. Multivariate analysis using a Cox model was completed for all factors with a p value <0.05 in univariate analysis. All statistical analysis was conducted in SPSS® v 19.0 (SPSS, Inc., Chicago, IL, USA).

Table 1 Toxicity based on CTCAE v3.0

	Grade 1–2 patients (%)	Grade 3–4 patients (%)
Fever	21 (100)	0
Joint pain	2 (9.5)	0
Leukopenia	7 (33.3)	1 (4.8)
Platelets	6 (28.6)	0
Hypertriglyceridemia	4 (19)	0
AST elevation	3 (14.3)	0
ALP elevation	4 (19)	0

Table 2 Characteristics of 21 patients

	Value (%)
Gender	
Male	15 (71)
Female	6 (29)
Age (years)	
<65	12 (57)
≥65	9 (43)
Primary location	
Colon	16 (76)
Rectum	5 (24)
Primary lymph node	
Negative	9 (43)
Positive	12 (57)
No. metastases	
<10	11 (52)
≥10	10 (48)
Tumor size (cm)	
<5	15 (71)
≥5	6 (29)
CEA (ng/mL)	
<50	10 (48)
≥50	11 (52)
Liver metastases at diagnosis	
Synchronous	17 (81)
Metachronous	4 (19)
Previous chemotherapy	
No	13 (62)
Yes	8 (38)

Table 3 HAI and conversion characteristics of 21 patients

	HAI	Conversion	*p* value
Gender			
Male	10	5	0.41
Female	3	3	
Age (years)			
<65	7	5	0.53
≥65	6	3	
Primary location			
Colon	10	6	0.66
Rectum	3	2	
Primary lymph node			
Negative	5	4	0.47
Positive	8	4	
No. metastases			
<10	6	5	0.39
≥10	7	3	
Tumor size (cm)			
<5	9	6	0.59
≥5	4	2	
CEA (ng/mL)			
<50	5	5	0.27
≥50	8	3	
Liver metastases at diagnosis			
Synchronous	10	7	0.5
Metachronous	3	1	
Previous chemotherapy			
No	5	8	0.006
Yes	8	0	
Shrinkage ratio			
<30 %	8	0	0.006
≥30 %	5	8	

HAI hepatic arterial infusion

Results

Toxicity and catheter complication

We treated 21 patients with unresectable colorectal liver metastasis between January 2008 and December 2011 and experienced no adverse events ≥grade 4. All patients developed fever after the first drug administration; however, all were grade ≤1 and treated with nonsteroidal anti-inflammatory drugs. Although there was one case of drug discontinuation for 2 weeks due to grade 3 leukopenia, no changes in the amount of drug administration were noted. Other adverse events were rated ≤grade 2 (Table 1).

No port-system-related infection was found. Although there was one case of blocked catheter, we were able to reinsert the catheter after flushing with heparinized saline. HAI was terminated in one patient due to the occlusion of hepatic artery after the 53rd drug infusion. Catheters were used 16.8 times on average.

Response

Characteristics of the 21 patients were number of metastases ≥10 (48 %), synchronous metastases (81 %), and prechemotherapy treatment (38 %; Table 2). Based on the RECIST, the efficacy of therapy in patients (including those undergoing systemic chemotherapy) was categorized as partial response (PR) in 13 patients (61.9 %) and stable disease (SD) in 4 patients (19 %). Although there were no cases of complete response (CR), the rate of disease control was 81 %. Of the 13 patients previously nontreated, PR was seen in 10 (76.9 %) and SD was seen in 1 (7.7 %).

Characteristics of resection and complications

Hepatectomy was performed in eight patients (38.1 %). Median treatment duration until resection was three cycles

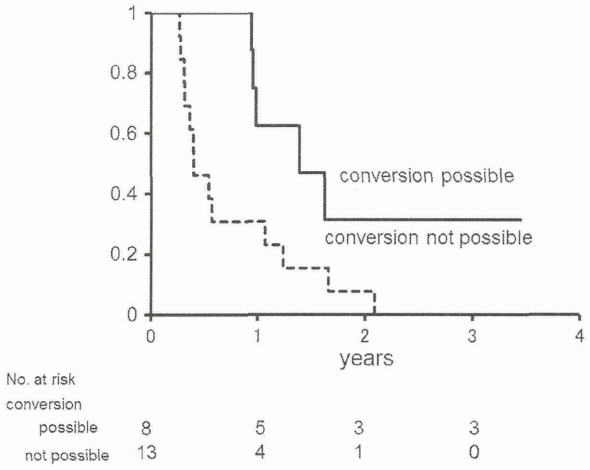

Fig. 1 Progression-free survival (PFS) of converted patients compared with patients not converted after treatment with HAI. Median PFS was 16.7 months versus 4.8 months, respectively ($p = 0.021$)

(range, 7–22 weeks of infusion). Patients who underwent conversion therapy had no prior history of chemotherapy and also had shrinkage in tumor size >30 % (Table 3). Median preoperative ICG R15 was 8 % (range, 7–17 %). Hepatectomy consisted of four cases of lobectomy + partial resection, four cases of partial resection (number of resections: 8, 7, 6, and 6), and six cases required RFA in addition to resection. One patient had a complication with postoperative bleeding and was treated successfully with hemostatic relaparotomy. There were no cases of mortality. The median duration of hospitalization was 12 days (range, 12–16 days).

Progression-free survival and overall survival

The median observation period was 31.2 months (range, 5.8–57.7 months). Median PFS and OS was 11.5 and 34.6 months, respectively. The median PFS in conversion and nonconversion cases to hepatectomy was 16.7 and 4.8 months, respectively (Fig. 1), with a significantly longer median PFS in the conversion cases ($p = 0.021$). In addition, the median OS was 48.4 and 26.6 months in conversion and nonconversion cases, respectively, with significantly longer median OS in the conversion cases ($p = 0.003$; Fig. 2). The median PFS in responders and non-responders was 16.9 and 5.2 months, respectively ($p = 0.005$), and the median OS was 45.2 and 24.1 months, respectively ($p = 0.0004$).

Prognostic factor analysis

Univariate analysis of PFS revealed that ≥10 metastases; tumors with diameter ≥5 cm and reduction in tumor size ≤30 % were poor prognostic factors. Hepatectomy was found to be a good prognostic factor. We performed multivariate analysis to obtain preliminary data even though the number of cases was small. More than ten metastases was the only poor prognostic factor in multivariate analysis [hazard ratio (HR) 32.21, $p = 0.003$; Table 4]. With regard to OS, hepatectomy was a good prognostic factor, and poor prognostic factors were ≥65 years of age, ≥10 metastases, tumors with diameter ≥5 cm, and reduction in tumor size ≤30 %. Multivariate analysis found a significant tendency for the number of metastases (HR 9.13, $p = 0.07$) and hepatectomy (HR 0.08, $p = 0.09$) to serve as prognostic factors (Table 5).

Discussion

Hepatic arterial infusion therapy has long been used as a local treatment for liver disease. In unresectable colorectal liver metastases, HAI is used as first-line therapy or conversion therapy following hepatectomy [12]. In recent years, HAI has been combined with systemic chemotherapy [13]; FUDR, 5FU, MMC, oxaliplatin, and irinotecan have been used as drugs of choice in HAI. In the present study, we performed immunochemotherapy using 5-FU and IFN. IFN, through its BCM of 5-FU, augments the antitumor activity of 5-FU by enhancing the inhibition of 5-FU on thymidylate synthase mRNA and thymidine kinase. In addition, as shown with the administration of IL-2, IFN increases the activity of immunocompetent cells in liver sinusoids, such as Kupffer and natural killer cells [14, 15]. We used PEG-IFNα-2a, which was constructed by fusing recombinant IFNα-2a synthesized in *E. coli* with a 40-kD polyethylene glycol (PEG) polymer. The high molecular weight of PEG reduces renal clearance of IFN,

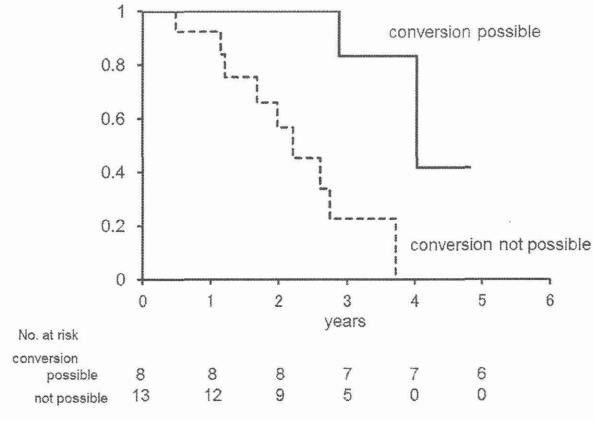

Fig. 2 Overall survival (OS) of converted patients compared with patients not converted after treatment with HAI. Median OS was 48.4 months versus 26.6 months, respectively ($p = 0.003$)

Table 4 Prognostic factors for progression free survival by univariate and multivariate analysis

	Univariate			Multivariate		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Gender						
Male/female	0.92	0.33–2.61	0.88			
Age (years)						
≥65/<65	1.39	0.54–3.55	0.5			
Primary location						
Colon/rectum	0.53	0.17–1.69	0.28			
Primary lymph node						
Positive/negative	1.21	0.47–3.11	0.7			
No. metastases						
≥10/<10	26.93	3.26–222.42	0.002	32.21	3.23–321.08	0.003
Tumor size (cm)						
≧5/<5	3.87	1.3–11.56	0.015	1.54	0.49–5.30	0.49
CEA (ng/mL)						
≥50/<50	2.48	0.95–6.44	0.06			
Liver metastases at diagnosis						
Synchronous/metachronous	0.46	0.13–1.67	0.24			
Previous chemotherapy						
Yes/no	1.51	0.59–3.86	0.39			
Shrinkage ratio (%)						
<30/≥30	4.15	1.42–12.17	0.009	1.98	0.53–7.37	0.31
Liver resection						
Yes/no	0.31	0.11–0.88	0.03	0.44	0.11–1.82	0.25

HR hazard ratio, *CI* confidence interval

most likely leading to an increase in IFN's systemic exposure time [16]. Moreover, the rate of IFN absorption is reduced because of the high molecular weight. At the time of intravenous administration, the time to reach maximum blood concentration and the average absorption rate of PEG-IFNα-2a were 78 and 59 h, respectively, considerably longer than the 10 and 2.6 h, respectively, seen with regular IFNα [17].

The toxicity of 5FU/PEG-IFNα-2a was surprisingly low, with only one case of temporary drug discontinuation. This is thought to be because of the smaller dosage of 5-FU (500 mg/m^2/week) used compared with conventional continuous infusion or bolus administration [12]. No adverse side effects of IFN, such as fatigue or psychiatric symptoms, were observed, thus demonstrating the safety of 5FU/PEG-IFNα-2a in HAI.

Although ≥20 % of HAI cases are associated with the occlusion of catheter and port-related problems [18–20], very few problems were observed in the present study. Reasons for this absence may include improvements of indwelling catheterization methods and catheter materials, particularly in recent years, as well as the handling skills of the ports. The short 90-min administration time in this study must also have helped.

In HAI of 5FU/PEG-IFNα-2a, the rate of response was 61.9 %. The response rate of HAI with IFNα-2b and DSM, which was used to enhance the concentration in tumor tissue, has been reported as 69.4 % [6]. Furthermore, the response rate was 78 % with coadministration of IL-2 [4]. Compared with these studies, the response rate seen in this study was slightly poor, which might be because 38 % of our patients had been undergoing systemic chemotherapy before the study, and prior treatment reduces the response rate as shown in a previous study [21].

Since the early 1990s in the United States and Europe, conversion therapy, which proactively uses hepatectomy when unresectable colorectal liver metastases are reduced in size after systemic chemotherapy, has become widespread. According to Bismuth et al., the 5-year survival rate of hepatectomy cases with initially unresectable metastases was as high as 40 % [22] and was not significantly different from that of resectable cases. On the other hand, the conversion rate was low at 16 %. Since then, many different regimens, for example, that use molecular target drugs in systemic chemotherapy have been employed, and the conversion rates have always been approximately 10–20 % [23–26], or more recently 38 % [27]. The conversion rate of HAI using 5FU/PEG-IFNα-2a

Table 5 Prognostic factors for overall survival by univariate and multivariate analysis

	Univariate			Multivariate		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Gender						
Male/female	1.42	0.41–4.94	0.58			
Age (years)						
≥65/<65	5.86	1.37–25.05	0.02	2.31	0.26–20.21	0.45
Primary location						
Colon/rectum	0.2	0.03–1.6	0.13			
Primary lymph node						
Positive/negative	1.94	0.56–6.71	0.29			
No. metastases						
≥10/<10	7.47	1.53–36.54	0.01	9.13	0.81–103.06	0.07
Tumor size (cm)						
≥5/<5	10.66	2.1–54.15	0.004	0.99	0.18– 7.27	0.99
CEA(ng/mL)						
≥50/<50	3.25	0.85–12.33	0.08			
Liver metastases at diagnosis						
Synchronous/metachronous	0.66	0.14–3.13	0.6			
Previous chemotherapy						
Yes/no	2.08	0.6–7.24	0.25			
Shrinkage ratio (%)						
<30/≥30	11.19	2.19–57.29	0.004	3.42	0.59–19.82	0.17
Liver resection						
Yes/no	0.08	0.01–0.65	0.02	0.08	0.01–1.46	0.09

HR hazard ratio, *CI* confidence interval

was high at 38.1 %, showing that HAI provides good local control of liver function. In this study, post-HAI ICG R15 was ≤10 and thus considered fair. Because the treatment does not affect hepatic function, it is expected to further improve conversion rate with the use of PVE and two-stage hepatectomy.

There are various reports on chemotherapy-related liver toxicity and complications from conversion therapy, and hepatic impairment, such as sinusoidal obstruction [28, 29] and chemotherapy-associated steatohepatitis (CASH) [30], have been observed in many clinical cases. Vauthey et al. [31] reported that the rate of complications after hepatectomy was 27 %, and when steatohepatitis was present, the rate of mortality within 90 days was 14.7 %. The rate of complications after the infusion of 5FU/PEG-IFNα-2a was low. There were no cases of mortality, and the period of administration was as short as 12 days. Because with three cycles of HAI, the therapy period was completed in a short time of 12 weeks, and this likely had less affect on liver function.

The median OS after the infusion of 5FU/PEG-IFNα-2a was relatively long at 34.6 and 26.6 months in both conversion and nonconversion cases, respectively. In other studies performed after 2,000, median OS was <20 months [32, 33], but later it increased to as much as 24.4 months, as reported by Kemeny et al. [4]. In immunochemotherapy, Pohlen et al. [7] had a fair median OS of 26 months, and HAI of 5FU/PEG-IFNα-2a demonstrated similarly good outcomes.

On the other hand, current systemic chemotherapy uses 5-FU, irinotecan, oxaliplatin, and molecular target drugs only. Complete administration of these drugs normally extends OS, but median OS is still around 20 months [34]. However, pretreatment systemic chemotherapy was used in 38 % of cases in this study, and the median OS after the infusion of 5FU/PEG-IFNα-2a in nonconversion cases was 26.6 months. We believe that this high OS can be attributed to the addition of immunochemotherapy to existing chemotherapy and molecularly targeted therapy. This also means that treatment outcome can be improved by the addition of other therapeutic approaches, such as immunochemotherapy. A previous study reported a median OS of 41 months in conversion cases with a combination of HAI and systemic chemotherapy [21]. The median OS for the infusion of 5FU/PEG-IFNα-2a in conversion cases was 48.4 months.

Because having ten or more tumors was a poor prognostic factor, therapy for multiple liver metastases will be an important issue in future studies. Previous studies also reported the number of metastases and tumor size as prognostic factors [2]. In the hepatectomy cases in this study, median OS was clearly extended, although not significantly, indicating the efficacy of conversion therapy.

Conclusions

We successfully performed HAI of 5FU/PEG-IFNα-2a, and no life-threatening complications were observed, even after conversion to hepatectomy. We plan to accumulate more cases and perform a randomized, controlled trial to compare the cost-effectiveness of treatment and the QOL of patients between conventional systemic chemotherapy and the HAI immunochemotherapy used in this study.

Conflict of interest None

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