cer. Over the past decade, the results of clinical studies in patients with metastatic colorectal cancer have revealed substantial improvements in survival [1, 2]. 5-Fluorouracil (5-FU)-based chemotherapy is the mainstay of treatment for patients with metastatic colorectal cancer. Combinations of infusional 5-FU, leucovorin and oxaliplatin (FOLFOX) and infusional 5-FU, leucovorin and irinotecan (FOLFIRI), with or without molecular targeting agents, are considered standard treatments for metastatic colorectal cancer [1–5]. The order of combinations for first- and second-line treatment, for example FOLFOX followed by FOLFIRI or FOLFIRI followed by FOLFOX, does not affect patient survival [1]. However, 20–30% of patients do not proceed to second-line treatment [6]. Therefore, adequate and active first-line treatment is essential in the treatment of colorectal cancer. As exposure to active agents, i.e. 5-FU, oxaliplatin and irinotecan, rather than second-line therapy itself appears to predict improved survival [7], the 'up-front' administration of these 3 effective drugs may be the most effective means of improving outcomes. Consequently, several groups have investigated the triple-drug FOLFOXIRI regimen (5-FU, oxaliplatin and irinotecan) in patients with metastatic colorectal cancer to improve their prognosis [8, 9]. FOLFOXIRI resulted in significant increases in activity, efficacy and improvements in the long-term outcome. However, the triple-drug regimen causes further adverse effects [10, 11]. In particular, neurotoxicity is a common and frequent adverse event that diminishes the dose that can be administered [8, 12]. We hypothesized that alternating oxaliplatin and irinotecan would allow patients to benefit from concurrent treatment with all 3 drugs as soon as they were diagnosed with metastatic disease while allowing them to recover from the adverse events associated with each drug before its administration was repeated. The aim of this study was to explore the efficacy and safety of alternating regimens of 4 cycles of mFOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) in the first-line treatment of advanced colorectal cancer. Specifically, we wanted to evaluate the impact of this schedule on the dose-limiting neurotoxicity and diarrhea associated with oxaliplatin and irinotecan.

Methods

Eligibility Criteria

Patients with histologically proven, unresectable, advanced or metastatic colorectal cancer who had not received any previous treatment were eligible for the study if they met all of the following criteria: measurable disease, age ≥20 and ≤75 years, Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥3 months and adequate bone marrow, hepatic and renal function. Written informed consent was obtained from all patients prior to enrollment in the study. The ethical, medical and scientific aspects of the study were reviewed and approved by the ethics committees of each participating institution in the University Hospital Medical Information Network clinical trials registry (UMIN000001340). The study was conducted in accordance with the Declaration of Helsinki of 1975, revised in 2000.

Treatment Schedule

Patients received an alternating regimen of 4 cycles of mFOLFOX-6 (85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin on day 1 followed by 400 mg/m^2 bolus 5-FU and a 46-hour 2,400-mg/m^2 5-FU infusion every 2 weeks) followed by 4 cycles of FOLFIRI (oxaliplatin replaced with 150 mg/m^2 irinotecan on day 1). This schedule was repeated until unacceptable toxicity or progressive disease (PD) was observed. Treatment was administered until the observation of PD or unacceptable toxicity, withdrawal of consent, the physician's decision to terminate, or interruption of treatment for >14 days occurred. Dose modification was performed based on the hematological parameters and the degree of non-hematological toxicities. Chemotherapy was delayed until recovery if neutrophil counts decreased to <1,500/mm^3, platelet counts decreased to <75,000/mm^3, or significant persistent non-hematological toxicity occurred. The 5-FU dose was reduced to 300 (bolus) or 500 mg/m^2 (infusion) if grade 3/4 diarrhea, stomatitis, nausea/vomiting, anorexia, dermatitis, grade 4 neutropenia, or grade 3/4 thrombocytopenia occurred. Oxaliplatin was also reduced to 65 mg/m^2 for the same conditions, except for the occurrence of dermatitis; additionally, it was reduced in cases of persistent (15 days or longer) grade 2 neurotoxicity or temporary (8–14 days) grade 3 neurotoxicity. In cases of persistent (15 days or longer) grade 3 neurotoxicity or temporary grade 4 neurotoxicity, oxaliplatin was omitted from the regimen. The irinotecan dose was reduced to 130 mg/m^2 for the same reasons as described for oxaliplatin. The use of Ca/Mg treatment was not regulated as part of this protocol.

Endpoints

The primary endpoint of the study was the response rate (RR), and the secondary endpoints were progression-free survival (PFS), overall survival (OS) and adverse effects. During the 4 weeks before chemotherapy was initiated, all patients underwent the following: physical examination, complete blood cell count, hepatic and renal function tests, and chest and abdominal computed tomography or magnetic resonance imaging. A physical examination, hepatorenal function tests and blood counts were performed before each cycle. Patients were assessed before starting each 2-week cycle according to the National Cancer Institute Common Toxicity Criteria version 3 [13]. Tumor evaluation was performed every month for the first 3 months and then every 2 months thereafter using the Response Evaluation Criteria in Solid Tumors version 1.0 [14]. A complete response (CR) was defined as the disappearance of all known lesions and the absence of new lesions. A partial response (PR) was defined as a reduction of 30% or more in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions. Stable disease (SD) was defined as a reduction of <30% or an increase of <20% in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions.

PD was defined as an increase of ≥20% in the sum of the maximum tumor lengths of up to 10 known lesions or as the appearance of at least 1 new lesion.

Statistical Considerations

Using the binomial exact method (DSTPLAN) with a null RR of 40%, an expected RR of 60%, one-sided $\alpha = 0.05$ and power of 80%, 42 patients were needed for the study. Allowing that 10% of patients would be ineligible or drop out, the planned target number of patients was 47. The confidence interval (CI) for the RR was estimated by the exact method. The duration of survival was measured from the day of entry into the study, and the OS and PFS curves were calculated by the Kaplan-Meier method. A one-sided $p < 0.05$ was considered statistically significant at the statistical test of the primary endpoint. All statistical analyses were performed using Stata version 11 statistical analysis software (Stata, College Station, Tex., USA).

Results

Patient Characteristics

Between July 2007 and June 2008, 48 patients in 25 institutions in Japan were enrolled in this trial. Two of the patients did not meet the eligibility criteria: 1 did not undergo a prior imaging examination and the other had multiple active cancers. Forty-seven patients were treated with protocol therapy. Response, OS and PFS were assessed in 46 patients. The characteristics of 47 patients and those eligible for study inclusion are listed in table 1. The median number of administration cycles was 12 (range 1–47). Toxicity and tolerability were assessed with all 47 patients who received protocol therapy.

Efficacy

The overall RR as determined by the independent committee was 58.7% (95% CI 43.5–73.5), and it included 1 CR (2.1%) and 26 PRs (56.5%). The number of instances of SD and PD were 14 (30.4%) and 2 (4.3%), respectively; 3 (6.5%) patients were not evaluable (table 2). The tumor control rate (CR + PR + SD) was 89.1%. Irrespective of the order of treatment, the period from registration to the first evidence of progression on imaging analysis was defined as PFS. After a median follow-up of 27.5 months, the median PFS was 10.3 months in the 46 assessable patients (95% CI 7.5–11.9; fig. 1), and the median OS was 28.4 months in those patients (95% CI 22.5–35.7; fig. 2). The 1-, 2- and 3-year survival rates were 84.5% (95% CI 70.5–92.4), 60.2% (95% CI 44.4–72.7) and 32.9% (95% CI 17.8–48.8), respectively. Surgery was performed in 9 patients (19.6%) after treatment.

Table 1. Baseline patient characteristics

Characteristic	All cases (n = 47)
Age, years	
Median	66
Range	43–75
Gender	
Male	35 (74.5)
Female	12 (25.5)
Performance status	
0	38 (80.9)
1	9 (19.1)
Existence of a primary tumor	
Yes	19 (40.4)
No	28 (59.6)
Site of the primary tumor	
C	1 (5.3)
A	3 (15.8)
T	3 (15.8)
D	1 (5.3)
S	5 (26.3)
RS	1 (5.3)
Ra	2 (10.5)
Rb	3 (15.8)

Figures in parentheses are percentages. C = Cecum; A = ascending colon; T = transverse colon; D = descending colon; S = sigmoid colon; RS = rectosigmoid colon; Ra = rectum above the peritoneal reflection; Rb = rectum below the peritoneal reflection.

Table 2. Antitumor efficacy

Response	Full analysis set (n = 46)
CR	1 (2.2)
PR	26 (56.5)
SD	14 (30.4)
PD	2 (4.3)
NE	3 (6.5)
Overall response rate (CR + PR)	27 (58.7)
95% CI	43.9–73.5*

Figures in parentheses are percentages. NE = Not evaluable.
* One-sided $p = 0.0008$ (exact method with the null RR = 40%).

Toxicity and Tolerability

The 4 cycles of FOLFOX6 and the 4 cycles of FOLFIRI could each be prescribed alternatively, although there were some treatment delays because of adverse reactions. In the shortest case, only 1 cycle was completed because

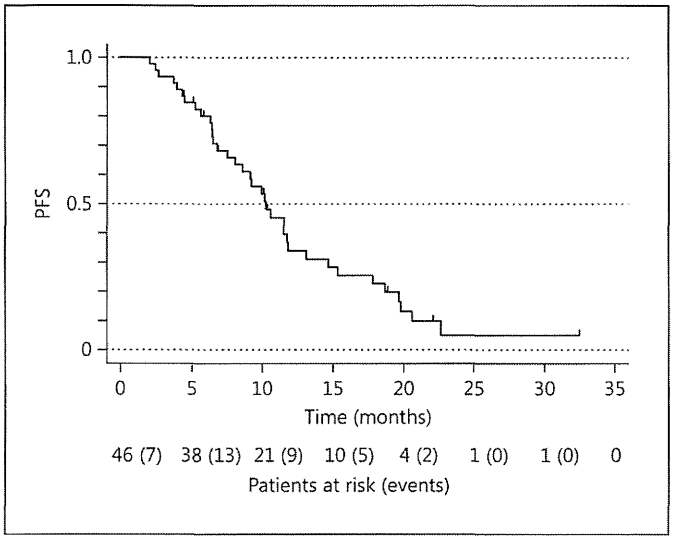

Fig. 1. Progression-free survival.

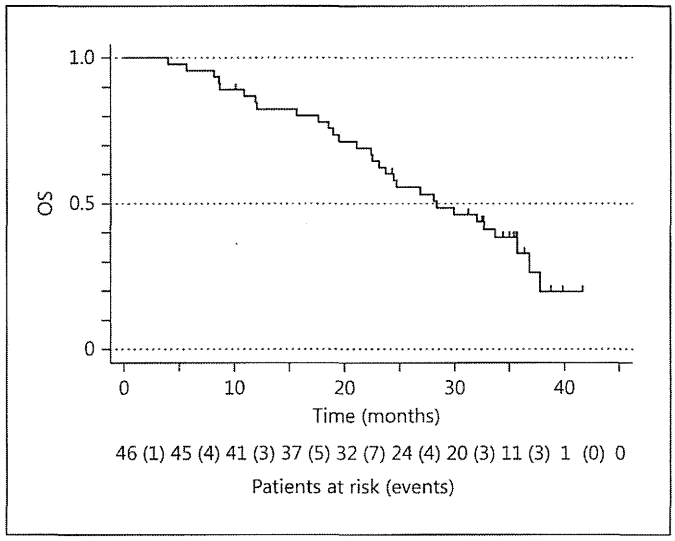

Fig. 2. Overall survival.

Table 3. Treatment-related adverse events

	All grades	G3	G4
Anorexia	32 (68.10)	4 (8.50)	0
Fatigue	27 (57.40)	2 (4.30)	0
Nausea	27 (57.40)	1 (2.10)	1 (2.10)
Mucositis	19 (40.40)	0	0
Constipation	17 (36.20)	0	0
Neurotoxicity (CTCAE)	17 (36.20)	0	0
Diarrhea	15 (31.90)	1 (2.10)	0
Alopecia	13 (27.70)	0	0
Vomiting	13 (27.70)	0	1 (2.10)
Fever	8 (17.00)	0	1 (2.10)
Hand-foot syndrome	6 (12.80)	0	0
Allergic reaction	4 (8.50)	0	0
Chromatosis	2 (4.30)	0	0
Febrile neutropenia	2 (4.30)	2 (4.30)	0
Insomnia	2 (4.30)	0	0
Pneumonia	2 (4.30)	1	0
Weight loss	2 (4.30)	0	0
Epistaxis	1 (2.10)	0	0
Gastrointestinal bleeding	1 (2.10)	0	0
Anemia	42 (89.40)	2 (4.30)	0
Neutropenia	41 (87.20)	17 (36.20)	9 (19.10)
AST elevated	39 (83.00)	3 (6.40)	0
Thrombocytopenia	35 (74.50)	2 (4.30)	0
ALT elevated	24 (51.10)	1 (2.10)	1 (2.10)
Total bilirubin elevated	9 (19.10)	0	0

Figures in parentheses are percentages.

of allergic reactions, whereas 47 cycles were completed in the longest case. The adverse events are shown in table 3. Among the 47 patients evaluated for toxicity, the most common grade 3–4 adverse events were leukopenia (26%), neutropenia (55%), anemia (4%), diarrhea (2%), febrile neutropenia (4%), nausea (4%), and vomiting (2%). No grade 3–4 neurotoxicity, which is a dose-limiting toxicity of oxaliplatin, was reported; only 1 case of grade 3–4 diarrhea was reported. Grade 3–4 hypersensitivity reactions were not reported. Figure 3 illustrates the occurrence of neurotoxicity for each patient in each cycle. Neurotoxicity occurred primarily during the FOLFOX cycles, although some of the neurotoxicity subsided during the FOLFIRI cycles.

Discussion

Among patients with unresectable colorectal cancers, the duration of survival has increased in the past decade. This improvement resulted primarily from the introduction of oxaliplatin or irinotecan into 5-FU-based regimens; additionally, molecular targeting agents have played a role in extending patient survival [1–5]. It is known that patient outcome is significantly improved with exposure to all active drugs in the course of disease treatment [1, 2]. Thus, the sequential administration of FOLFOX and FOLFIRI in any order with molecular targeting agents is the standard treatment for unresectable colorectal cancer [4, 5]. However, approximately 20–30%

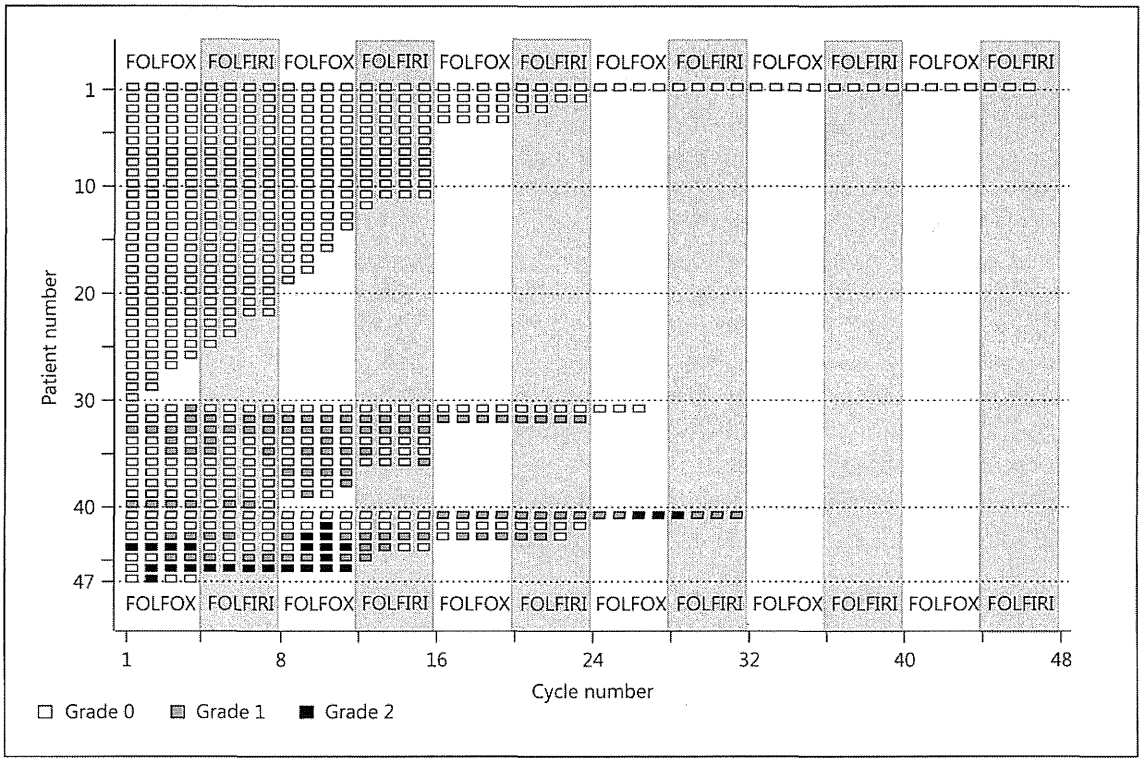

Fig. 3. Occurrence of neurotoxicity (CTCAE) in each cycle for all 47 patients. White squares indicate no toxicity; gray squares indicate grade 1 neurotoxicity; black squares indicate grade 2 neurotoxicity.

of patients exhibit PD after first-line therapy; hence, they do not receive further chemotherapy [6, 7]. Furthermore, an important limitation of this strategy is frequent grade 3 sensory neuropathy, which occurred in approximately one third of the patients initially treated using FOLFOX [15, 16]. This neuropathy forced many patients to stop oxaliplatin-containing treatment before tumor progression [1].

Three strategies have been proposed to avoid these toxicities and increase the rate of exposure to all active drugs. First, all 3 key drugs are administered during first-line therapy, as with the FOLFOXIRI regimen [8, 9, 12]. It is reported that combinations including irinotecan and oxaliplatin with 5-FU (FOLFOXIRI) are feasible. The principal benefit of the FOLFOXIRI regimen is its high RR; further, high liver resection rates have been reported. However, the toxicity of these drugs when given in combination results in dose reductions for each of the drugs [8, 10, 11].

The second strategy involves stop-and-go regimens such as the OPTIMOX series that include oxaliplatin-free intervals to reduce grade 3 sensory neuropathy [16]. This stop-and-go regimen avoided the problem of oxaliplatin-induced neurotoxicity by using a dose-intense FOLFOX7 regimen for a defined period, stopping the therapy before severe neurotoxicity developed, and later reintroducing the same regimen. This regimen was extremely useful for reducing the neurotoxicity of oxaliplatin; however, response and survival were not improved.

The third method involves alternating regimens such as 4 courses of FOLFOX and 4 courses of FOLFIRI, as investigated in this trial. To improve response and survival, other alternating regimens have been examined. Alternating oxaliplatin and irinotecan in association with the De Gramont regimen has been used in first- and second-line chemotherapy for metastatic colorectal cancer [17]. Seventy-nine patients with previously untreated, unresectable colorectal cancer were included in a study of this regimen as a first-line treatment. Treatment consisted of 5-FU/leucovorin plus oxaliplatin alternated biweekly with the same 5-FU/leucovorin regimen plus irinotecan. Treatment was maintained until tumor progression or unacceptable toxicity was noted. Grade 1 or 2 neurotoxicity was observed in 59% of cases, but no grade 3 and 4 neurotoxicity was observed. An objective RR of 54% was attained. The median time to progression and OS was 13

and 18 months, respectively. In another phase II study, GERCOR utilized an alternating regimen of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) as a second-line therapy in 39 patients with 5-FU-resistant unresectable colorectal cancer [18]. Eighteen patients had an objective response (46.1%). The median PFS and OS were 8.8 and 18.7 months, respectively. Only 2 patients (5.1%) exhibited grade 3 oxaliplatin-induced neuropathy. Another group evaluated an alternating XELFOX and XELFIRI regimen [19]. Treatment consisted of 2 consecutive days of 200 mg/m^2 leucovorin, 400 mg/m^2 5-FU and 2,000 mg/m^2 capecitabine in 1 cycle and the addition of 50 mg/m^2 oxaliplatin for 2 days before the combination treatment in the subsequent cycle.

To our knowledge, this study is the first to examine the efficacy and safety of an alternating regimen of 4 courses of FOLFOX6 followed by 4 courses of FOLFIRI in patients with non-pretreated metastatic colorectal cancer. The objective RR of 58.5% is better than that of the FOLFOX or FOLFIRI chemotherapy regimens without molecular targeting agents and is close to that of FOLFOXIRI chemotherapy [9]. This regimen might be a substitute for FOLFOXIRI which has a high rate of conversion to surgery. In our study, 9 (19.6%) patients were converted to surgery including liver resection. In addition, this strategy was implemented to increase the efficacy of treatment and extend survival. The median PFS and OS were 10.3 and 28.4 months, respectively. PFS for first-line FOLFOX6 or FOLFIRI treatment without molecular targeted agents was 8–10 months [1], and PFS increased to 10–14 months when second-line treatment was also administered. Therefore, PFS in this study was not long, although OS was extended. This survival may be partly influenced by the therapy that followed the treatment administered in the study. In this phase II study, because molecular targeted agents were not included in the protocol treatment, FOLFOX6 and FOLFIRI with molecular targeted agents were chosen as the second-line treatment. At present, oral fluoropyrimidine with molecular target agents were considered as a choice as a second therapy and the third therapy. Although survival was not a primary endpoint, the remarkably long OS associated with the FIREFOX regimen is noteworthy. Furthermore, the most remarkable result in this study was the low level of neurotoxicity. In particular, no grade 3–4 peripheral neurotoxicity was observed. Only 6 patients experienced grade 2 neurotoxicity. Figure 3 shows the occurrence of neurotoxicity in all patients. Neurotoxicity improved during the FOLFIRI cycles. This tendency was similar to that observed with the OPTIMOX regimen. However, the OPTIMOX regimen does not have a chemotherapy-free interval; therefore, PFS can be maintained well. In this phase II trial, only 6 (12.7%) patients did not receive FOLFIRI because of disease progression or patient refusal. The high usage rate for the 3 active drugs is advantageous for this regimen because 20–30% of patients cannot receive second-line chemotherapy because of disease progression. Therefore, this low level of neurotoxicity may have greatly contributed to the long PFS and OS in this study.

Our findings suggest that the alternating administration of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) is effective and well tolerated as a first-line treatment for metastatic colorectal cancer. A favorable toxicity profile and prolonged time to progression were observed. Based on this study, we recently conducted and finished another phase II study of 4 alternating cycles of FOLFOX6 and FOLFIRI with bevacizumab.

Disclosure Statement

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Adjuvant Hepatic Arterial Infusion Chemotherapy after Hepatic Resection of Hepatocellular Carcinoma With Macroscopic Vascular Invasion

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Abstract

Background The prognosis of hepatocellular carcinoma (HCC) with macroscopic vascular invasion is extremely poor even after hepatic resection. We aimed to clarify the efficacy of adjuvant hepatic arterial infusion chemotherapy (HAI) for HCC with vascular invasion.

Methods A total of 73 HCC patients with macroscopic vascular invasion were divided into two groups: 38 with hepatectomy with HAI (HAI group) and 35 with hepatectomy alone (non-HAI group). From 1997 to 2007, HAI was performed via an implanted injection port. The treatment comprised three courses of weekly infusion of HAI, which comprised cisplatin (10 mg daily on days 1–5) followed by 5-fluorouracil (5-FU; 250 mg daily on days 1–5) infusion. From 2007, cisplatin (60 mg/m^2), 5-FU (600 mg/m^2), and a mixture of mitomycin C (3 mg/m^2) and degradable starch microspheres were administered for two courses.

Results Overall, 92 % of patients completed adjuvant HAI. In the HAI and non-HAI groups, the 5-year disease-free survival (DFS) rates were 33.1 % and 11.8 %, respectively ($p = 0.029$), and the 5-year overall survival (OS) rates were 46.7 % and 32.7 %, respectively ($p = 0.318$). Among the patients with Vp3/4 or Vv3 ($n = 32$) in the HAI group, the 3-year DFS and OS rates were 33.7 % and 56.8 %, respectively ($p = 0.049$). Those in the non-HAI group were 8.3 % and 12.0 %, respectively ($p = 0.023$). Cox proportional multivariate analysis for DFS revealed that HAI was an independent favorable prognostic factor in all 73 patients (hazard ratio 0.536; $p = 0.029$).

Conclusions Adjuvant HAI for HCC patients with vascular invasion might reduce the risk of recurrence.

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide [1]. Hepatectomy achieves favorable outcomes in well-selected candidates and is still considered one of the most potentially curative treatments for HCC [2]. Unfortunately, the long-term survival after hepatectomy is unsatisfactory because of the high incidence of tumor recurrence, especially intrahepatic tumors [3]. After curative hepatic resection for HCC, the recurrence rates at 2 and 5 years are approximately 50 % to 60 % and 80 %, respectively [4–6]. The prognosis remains extremely poor in those with advanced HCC with distinct vascular invasion, such as tumor thrombosis of the first branch or trunk of the portal vein or inferior vena cava [7, 8]. Portal vein tumor thrombosis (PVTT) can cause widespread dissemination of tumor cells via the portal tract as well as liver dysfunction and portal vein hypertension. In turn, this can lead to intractable ascites, variceal rupture, hepatic encephalopathy, and/or death [9]. The risks of PVTT with intrahepatic dissemination after local ablation therapy—e.g., ethanol injection therapy, microwave coagulation therapy, radiofrequency ablation—for small HCCs adjacent to the main or sectional portal vein were recently

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reported [10]. However, even with the removal of a macroscopic PVTT, there may still be microscopic tumor thrombi, which can be the source of a recurrence. Thus, an effective adjuvant therapy is required to prevent tumor recurrence after hepatic resection treatments for patients with vascular invasion.

Recent advances in implantable drug delivery systems have facilitated repeated hepatic arterial infusion of chemotherapy (HAI). Several studies report that intraarterial 5-fluorouracil (5-FU) with low-dose cisplatin [7, 11, 12] or 5-FU and systemic interferon (IFNα) [13] are the most effective combinations for unresectable HCCs with PVTT. However, there is little convincing evidence indicating that adjuvant therapy reduces the risk of recurrence after hepatic resection. Furthermore, no standard regimen has been established.

In the present study, we assessed the efficacy and feasibility of intraarterial cisplatin/5-FU combination therapy for surgically resected HCCs with massive vascular invasion. We identified patients subsets who would most likely benefit from adjuvant HAI.

Methods

From April 1997 to March 2011, a total of 539 patients underwent hepatic resection for HCC at Kumamoto University Hospital. Among them, the 77 patients who underwent resection of HCC with macroscopic vascular invasion (≥Vp2 or ≥Vv2) and without distant metastasis were enrolled in this study. The invasion sites of portal venous invasion (Vp) and hepatic venous invasion (Vv) were defined as follows: Vp2, second-order branches of the portal vein; Vp3, first-order branches of the portal vein; Vp4, main trunk or opposite the first branch of the portal vein; Vv2, main trunk of the hepatic vein; Vv3, inferior vena cava. Portal or hepatic venous invasion was diagnosed based on the findings of preoperative imaging studies, such as dynamic computed tomography (CT) or magnetic resonance imaging (MRI) and CT angiography. The diagnosis of HCC was confirmed by histopathological examinations of the resected specimens.

The entry criteria of HAI group were as follows: no recurrence confirmed 1 month after hepatic resection; appropriate liver function reserve; good performance status; sufficient recovery from the operation. Four patients died because of postoperative complications (liver failure 2; acute respiratory distress syndrome 1; intraabdominal infection 1) and were excluded from analysis. The remaining 73 patients were reviewed retrospectively. In all, 38 patients treated with hepatic resection and HAI were allocated to the HAI group. During the same period, 35 patients who underwent hepatic resection without HAI therapy by the same surgical team were allocated to the non-HAI group. The reasons why patients did not receive HAI were as follows: early recurrence ($n = 10$), disapproval of the therapy ($n = 10$), advanced age ($n = 4$), co-morbidities ($n = 7$), poor performance status ($n = 4$).

Patients diagnosed with multiple and hypervascular tumor recurrence in the remnant liver on CT angiography 1 month after hepatic resection ($n = 10$) were treated with transarterial chemoembolization (TACE) using cisplatin suspended in Lipiodol with a gelatin sponge instead of HAI according to our treatment strategy [14]. This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies of the Ministry of Health, Labor, and Welfare in Japan. Written informed consent was obtained from all patients.

Surgical technique

All patients underwent hepatic resection performed by two senior liver surgeons. The operative procedure was determined beforehand on the basis of the liver function reserve, the extent of the main and satellite tumors, and portal or venous invasion. Parenchymal dissection was performed using an ultrasonic surgical aspirator (CUSA; Valley Lab, Boulder, CO, USA) and bipolar forceps with intermittent clamping of the portal triad. After 2005, we preferred a precoagulation technique using a dissecting sealer (Valley Lab) or the VIO soft coagulation system (ERBE, Elektromedizin GmbH, Tübingen, Germany) [15]. For the patients with Vp4, the PVTT was removed using the "peeling off" technique [16]. In brief, the portal venotomy was placed after adequate vascular control of the portal flow was established. The PVTT was dissected from the portal venous wall and removed via the opening. Macroscopic residual PVTTs intruding into tiny branches were extracted meticulously. A multiperforated drain was placed in the abdominal cavity at the end of the procedure.

HAI treatment

From 1997 to 2007, patients with HCCs were treated by arterial infusion of a chemotherapeutic agent via a subcutaneously implanted injection port (old protocol). In principle, a hepatic arterial catheter was placed 2 to 3 weeks after the operation via the femoral artery. Celiac angiography was performed according to the Seldinger technique. A 4For 5F heparin-coated catheter was introduced into the proper or common hepatic artery. The gastroduodenal and right gastric arteries were occluded using a steel coil to prevent gastroduodenal injury caused by anticancer agents. After the catheter was connected to the injection port, the device was implanted in a subcutaneous pocket in the right lower quadrant to avoid catheter kinks. One course consisted of cisplatin administration (10 mg daily on days 1–5) and subsequent infusion of 5-FU (250 mg daily on days 1–5). After confirming a lack of recurrence in the remnant

liver by CT angiography 4 weeks after surgery, HAI was started and repeated for 3 courses. The injection port was removed 1 week after the end of HAI with confirmation of a lack of recurrence.

From 2007, patients with HCC were treated without an injection port (new protocol). Briefly, a 4F or 5F heparin-coated catheter was introduced into the proper hepatic artery. Cisplatin (60 mg/m^2) dissolved in 100 ml saline for 10 min followed by 5-FU (600 mg/m^2) in 100 ml saline for 10 min were injected into the proper and more distant hepatic arteries, respectively. Then, mitomycin C (3 mg/m^2) dissolved in 3 to 5 ml of saline mixed with 3 to 5 ml of degradable starch microspheres (DSMs) (Spherex; Yakult, Tokyo, Japan) was administered. This procedure was repeated twice at 4 weeks after surgery with a 1-month interval.

Follow-up

The follow-up program included serum α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonists-II (PIVKA-II) assays every 1 to 2 months. Imaging follow-up was performed using transabdominal ultrasonography (US) examination or computed tomography (CT) every 3 to 4 months. Magnetic resonance imaging (MRI) was performed when deemed necessary. During follow-up, if recurrence was recognized the patient was treated with a second hepatectomy, TACE, radiofrequency ablation, radiotherapy, or chemotherapy.

Data collection

Information on 15 variables was collected for each patient as potential risk factors for recurrence and predictors of survival. The extents of vascular involvement and tumor differentiation were confirmed in the resected specimen. Segmentectomy of ≥3 was defined as a major hepatic resection. Others were defined as minor hepatic resections. The continuous variables of age, indocyanine green retention at 15 min (ICG-R15), main tumor size, and serum AFP and PIVKA-II levels were categorized by cutoff values according to their median values: 64 years, 10 %, 60 mm, 70.2 ng/ml, and 697 IU/ml, respectively.

Statistical analyses

Student's t test, the χ^2 test,or Fisher's exact test was used where appropriate to compare the clinical and histologic parameters between the two groups. The cumulative survival curves were obtained using the Kaplan–Meier method. Survival curves were statistically compared using the log-rank test. Univariate analysis of the data from all cases was performed. Variables that exhibited statistical significance in the univariate analysis were subsequently included in the multivariate analysis, which was performed using Cox proportional hazard analysis. For all tests, the level of significance was set at $p < 0.05$.

Results

The clinical and pathological characteristics of the patients are summarized in Tables 1 and 2. The mean age was significantly lower in the HAI group than in the non-HAI group. The rate of poor differentiation was significantly higher in the HAI group than in the non-HAI group. However, there were no significant differences between the

Table 1 Clinical profile and serologic assays for HCC patients who underwent surgery: HAI group versus non-HAI group

Parameter	HAI group (n = 38)	Non-HAI group (n = 35)	p
Age (years)	61.8 ± 8.8	65.7 ± 8.8	0.036
Sex (M/F)	34/4	28/7	NS
Hepatitis[a]	16/13/0/9	7/21/1/6	NS
Albumin (g/dl)	4.0 ± 0.5	3.8 ± 0.4	NS
Total bilirubin (mg/dl)	0.75 ± 0.2	0.77 ± 0.2	NS
Prothrombin activity (%)	90.8 ± 13.5	95.1 ± 11.9	NS
Platelet count (×10^4/μl)	13.4 ± 7.3	15.3 ± 12.5	NS
Child Pugh score (A/B)	38/0	34/1	NS
ICG-R15 (%)	13.4 ± 7.3	15.3 ± 12.5	NS
AFP (ng/ml)	97.6 (3–292,829)	55.5 (1.6–474,000)	NS
AFP-L3 (≥10 %/<10 %)	15/23	17/18	NS
PIVKA-II (mAU/ml)	504 (11–18574)	1211 (0–298,050)	NS
Tumor size (mm)	66.6 ± 39.3	70.0 ± 42.3	NS
Multiple tumors (yes/no)	25/13	23/12	NS

HCC hepatocellular carcinoma, *HAI* hepatic arterial infusion chemotherapy, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibodies, *ICG-R15* indocyanine green retention rate at 15 min, *AFP* α-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonists II

[a] Including the following: HBsAg$^+$/HCVAb$^+$; both positive; both negative

Table 2 Perioperative results and histologic findings for HCC patients who underwent surgery: HAI group versus non-HAI group

Parameter	HAI group ($n = 38$)	Non-HAI group ($n = 35$)	p
Operating time (min)	492 ± 131	481 ± 105	NS
Blood loss (ml)	1079 ± 882	1009 ± 965	NS
Blood transfusion (±)	14/24	11/24	NS
Type of resection (major/minor)	30/8	26/9	NS
UICC stage 2/3A/3B/4A	3/8/25/2	4/10/19/2	NS
Tumor differentiation (well to moderate/poor/unknown)	14/23/1	22/12/1	0.023
Tumor type (simple nodular/others)	21/17	15/20	NS
Surgical margin (∓)	33/5	32/3	NS
Portal venous invasion (Vp0 ~ 1/2/3/4)	7/14/14/3	8/16/9/2	NS
Hepatic venous invasion (Vv0 ~ 1/2/3)	26/11/1	21/12/2	NS

UICC stage: International Union against Cancer staging

HAI and non-HAI groups with respect to any other variable. The surgical parameters including operative procedure, operative duration, and blood infusion rates, were comparable between the two groups.

Compliance and side effects of chemotherapy and hepatic resection

A total of 35 patients (92 %) completed HAI after hepatic resection. The side effects of adjuvant HAI (according to CTCAE v4.0) are shown in Table 3 .HAI was stopped because of tumor recurrence, grade 4 neutropenia, and therapy refusal in one patient each. No lethal side effects of HAI were observed. Five patients (13 %) experienced grade 3/4 adverse events. Three patients had grade 3 vomiting, and three had severe neutropenia (one with grade 4, two with grade 3). One patient (4.1 %) developed a hepatic arterial occlusion caused by the implanted catheter. Among all 73 patients, postoperative complications occurred in 21 (28.7 %): significant pleural effusion or ascites in 7, bile leakage in 3, surgical-site infection in 3, liver failure in 2, abdominal abscess in 2, intraabdominal bleeding in 1, duodenal ulcer in 1, wound dehiscence in 1, and cholangitis in 1.

Table 3 Side effects of adjuvant HAI ($n = 38$)

Side effect	All	Grade3/4
Neutropenia	9 (23.7 %)	3 (7.9 %)
Thrombocytopenia	3 (7.9 %)	0
Vomiting	8 (21.0 %)	3 (7.9 %)
Poor appetite	5 (13.1 %)	0
Ascites	1 (2.6 %)	0
Acute kidney injury	1 (2.6 %)	0
Bilirubin	5 (13.1 %)	0
Hepatic arterial occlusion	1 (2.6 %)	–

Tumor recurrence

At a median follow-up of 25 months (range 3–149 months), 23 (60.5 %) and 29 (82.8 %) patients in the HAI and non-HAI groups, respectively, developed tumor recurrence. The rate of recurrence in the remnant liver in the HAI group was 31.5 %, which was significantly lower than 68.5 % in the non-HAI group ($p = 0.001$). Extrahepatic recurrence rates were not significantly different between the two groups ($p = 0.360$). In all, 45 patients—20 (52.6 %) in the HAI group and 25 (71.4 %) in the non-HAI group—developed recurrence within 2 years after hepatic resection, but the recurrence rates within 2 years were similar between the two groups ($p = 0.098$).

Disease-free and overall survival

There was no significant difference in recurrence or survival rates between the patients who received HAI according to the old ($n = 25$) and new ($n = 13$) protocols: 3-year disease-free survival (DFS) 55.0 % vs. 50.0 %; 3-year overall survival (OS), 53.0 % vs. 54.2 %). Both the 3- and 5-year DFS rates were 33.1 % for patients treated with HAI and 11.8 % for patients in the non-HAI group. The HAI group achieved significantly better outcomes than the non-HAI group ($p = 0.029$) (Fig. 1a). The 3- and 5-year OS rates were 56.2 % and 46.7 % in the HAI group and 37.4 % and 32.7 % in the non-HAI group, respectively ($p = 0.318$) (Fig. 1b).

Univariate analysis for DFS and OS was performed for the 73 patients with macroscopic vascular invasion. Tumor size, number of tumors, International Union Against Cancer stage (UICC, 7th edition), and HAI were recognized as potential prognostic factors for DFS (Table 4). AFP, tumor size, and the degree of vascular invasion were recognized as potential prognostic factors for OS (Table 5). Multivariate analysis revealed that the number of tumors [hazard ratio (HR) and 95 % confidence interval (CI): 2.246 (1.158–4.359)] and HAI [HR and 95 % CI): 0.536 (0.306–0.940)] were

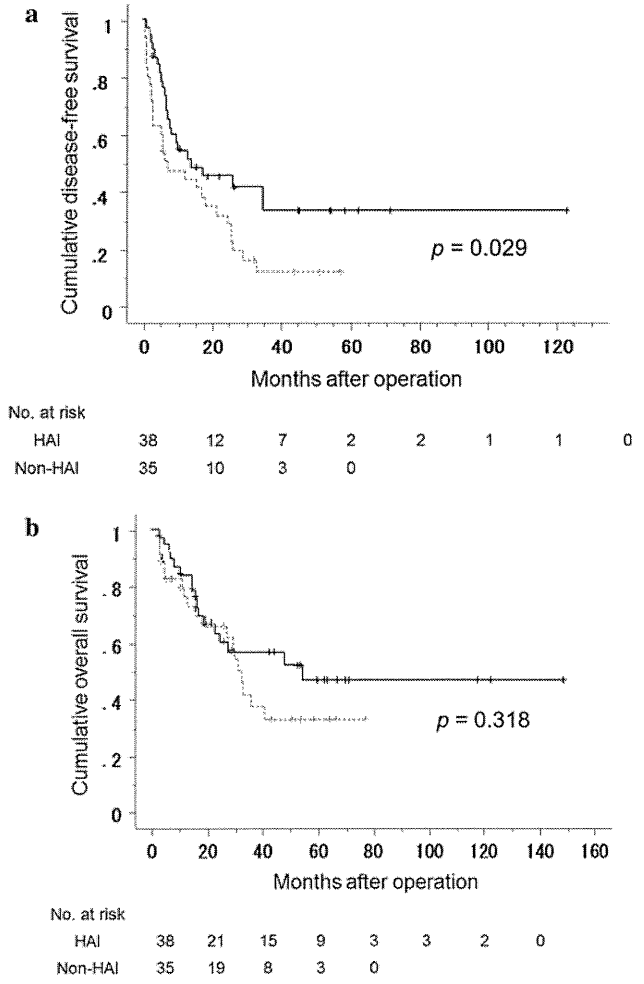

Fig. 1 **a** Disease-free survival (DFS) curves after hepatic resection with or without hepatic arterial infusion (*HAI*) chemotherapy in 73 patients. The HAI group (*solid line*) exhibited significantly better DFS than the non-HAI group (*dashed line*) ($p = 0.029$). **b** Overall survival (OS) curves after hepatic resection in the HAI (*solid line*) and the non-HAI groups (*dashed line*) in 73 patients. There was no significant difference between the two groups with respect to OS ($p = 0.318$)

independent factors for DFS (Table 6). Only tumor size of ≥60 mm was an independent prognostic factor for OS in the multivariate analysis ratio [HR and 95 % CI: 2.296 (1.106–4.767); $p = 0.025$].

On the other hand, among the limited patients with Vp3/4 or Vv3 ($n = 32$), the 3-year DFS and OS rates were 33.7 % and 56.8 % in the HAI group and 8.3 % and 12.0 % in the non-HAI group, respectively (Fig. 2). The HAI group had significantly better DFS and OS than the non-HAI group ($p = 0.023$ and 0.049, respectively). However, among patients with Vp2 or Vv2, the 3-year DFS and OS rates were 32.6 % and 57.0 % in the HAI group and 13.7 % and 52.0 % in the non-HAI group, respectively. There were no significant differences between these two groups.

Table 4 Univariate analysis for disease-free survival ($n = 73$)

Factor	Median DFS (months)	p
Age (years)		0.770
<64	9.5	
≥64	15.4	
Sex		0.961
Male	17.4	
Female	27.2	
Tumor size (mm)		0.035
<60	18.0	
≥60	6.4	
Tumor number		0.006
Solitary	33.0	
Multiple	7.9	
Operative method		0.309
Minor	16.8	
Major	9.5	
ICG-R15 (%)		0.431
<10	12.3	
≥10	15.4	
AFP (ng/ml)		0.704
<70.2	13.0	
≥70.2	15.4	
PIVKA-II (mAU/ml)		0.105
<697	17.3	
≥697	6.5	
UICC stage		0.002
2 or 3A	6.5	
3B or 4	33.0	
Tumor differentiation		0.816
Well to moderately	13.0	
Poor	8.4	
Vascular invasion		0.349
Vp2, Vv2	14.0	
Vp3-4, Vv3	6.5	
Tumor type		0.199
Simple nodular	24.7	
Others	9.5	
Blood transfusion		0.176
Yes	6.4	
No	16.8	
Stage of fibrosis[a]		0.290
F0–II	24.7	
FIII–IV	7.9	
HAI		0.029
Yes	14.0	
No	7.2	

DFS disease-free survival

[a] New Inuyama classification [35]

Table 5 Univariate analysis for OS ($n = 73$)

Factors	Median survival (months)	p
Age (years)		0.972
<64	33.3	
≥64	33.0	
Sex		0.961
Male	17.4	
Female	27.2	
Tumor size (mm)		0.023
<60	–	
≥60	27.2	
Tumor number		0.067
Solitary	–	
Multiple	30.0	
Operative method		0.919
Minor	31.6	
Major	33.3	
ICG-R15 (%)		0.473
<10	13.3	
≥10	19.7	
AFP (ng/mL)		0.032
<70.2	–	
≥70.2	33.0	
PIVKA-II (mAU/ml)		0.080
<697	54.8	
≥697	27.2	
UICC stage		0.880
2 or 3A	36.4	
3B or 4	33.0	
Tumor differentiation		0.761
Well to moderately	33.3	
Poor	54.8	
Vascular invasion		0.025
Vp2, Vv2	48.3	
Vp3-4, Vv3	19.7	
Tumor type		0.689
Simple nodular	54.8	
Others	33.0	
Blood transfusion		0.088
Yes	24.8	
No	41.3	
Stage of fibrosis[a]		0.256
F0–II	48.3	
FIII–IV	31.6	
HAI		0.318
Yes	54.8	
No	31.6	

[a] New Inuyama classification [35]

Table 6 Multivariate analysis for DFS

Factor	p	HR	95 % CI
Tumor size	0.091	1.623	0.925–2.849
Multiple tumors	0.017	2.246	1.158–4.359
HAI	0.029	0.536	0.306–0.940

HR: hazard ratio; CI: confidence interval

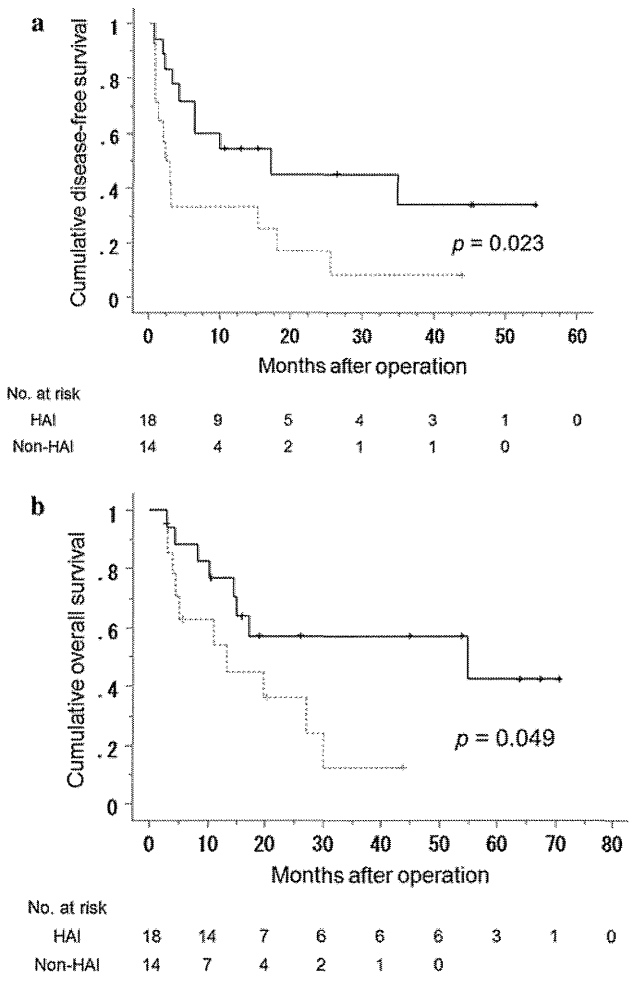

Fig. 2 **a** DFS curves after hepatic resection with or without HAI for the patients with Vp3/4 or Vv3 ($n = 32$). The HAI group (*solid line*) showed significantly better DFS than the non-HAI group (*dashed line*) ($p = 0.023$). **b** OS curves after hepatic resection with or without HAI for the patients with Vp3/4 or Vv3 ($n = 32$). The HAI group (*solid line*) showed significantly better OS than the non-HAI group (*dashed line*) ($p = 0.049$)

Discussion

The prognosis of HCC patients with apparent PVTT is limited to a few months after diagnosis [8, 17–19]. Although hepatic resection as a monotherapy demonstrates

relatively favorable 5-year survival rates (4.0–28.5 %) and median survival times (6–14 months), the recurrence rates are extremely high [20–24]. Portal venous invasion is the most significant risk factor for the early postoperative recurrence of HCC [25]. Therefore, other novel strategies to prevent recurrence are required. At present, combined treatment consisting of hepatic resection and TACE or HAI shows the most promising results. The 5-year survival rate and median survival time for TACE followed by hepatic resection are 42 % and 31 months, respectively [26]. For hepatic resection followed by HAI, these numbers are 36 % and 22 months. respectively [11].

Accordingly, in 1997 we initially started the protocol of arterial infusion of cisplatin (total 150 mg) followed by 5-FU (total 3750 mg). The rationale behind this treatment regimen is that cisplatin and 5-FU have an antitumor effect. Moreover, cisplatin has a synergistic effect as a modulator for 5-FU, and cisplatin and 5-FU can be administered at low doses to reduce adverse reactions. The treatment duration of our protocol—three courses of low-dose cisplatin plus 5-FU—is shorter than that reported in the literature. However, it may be sufficient to reduce the risk of recurrence because of the favorable prognosis of our treatment. The 3-year DFS and OS were 55.0 % and 53.0 %, respectively, which are comparable to those reported in the literature [27–29]. Nevertheless, one patient developed hepatic arterial occlusion caused by the implanted catheter.

Based on this experience, in 2007 we initiated a new protocol without an injection port: two rounds of one-shot HAI consisting of cisplatin (60 mg/mm^2 per 10 min), 5-FU (60 mg/mm^2 per 10 min) followed by mitomycin-C (3 mg/mm^2) with DSM. In the new protocol, we used arterial administration using DSM and mitomycin-C. DSM is a micro-embolic material made from potato starch, $45 \pm 7 \times 10^{-6}$ mm in diameter, that induces transient occlusion of small arteries for 1 h [30]. Co-administration of an anticancer drug with DSM reduces drug dilution because of hepatic arterial flow and enhances drug retention in tumors better than with a single bolus injection [30]. We adopted DSM rather than permanent embolic materials to decrease the damage to the remnant liver during the early postoperative period (4–8 weeks after surgery).

A retrospective case–control study of 127 HCC patients demonstrated that adjuvant chemolipiodolization following hepatic resection is an independent prognostic factor for 2-year recurrence-free survival [HR and 95 % CI: 0.55 (0.34–0.90); $p = 0.02$] compared to hepatic resection alone [3]. However, the ratio of vascular involvement patients in that study was only 19 % [3]. In a randomized controlled manner, 126 HCC patients with PVTT were divided into control and TACE groups [27]. The control group underwent surgery and PVTT removal, and the TACE group underwent the same procedure combined with postoperative adjuvant TACE. The median survival time of 13 months and a 5-year survival rate of 21.5 % in the TACE group were significantly greater than the corresponding values of 9 months and 8.5 % in the control group [27]. The treatment was started 3 to 4 weeks after surgery and was repeated once every 1 to 2 months for two to five courses (mean 1.8). This postoperative adjuvant TACE resulted in significantly greater OS. The starting point and total course of adjuvant therapy were similar to those of our new protocol during the late period (beginning at 4 weeks for a total of two courses).

Despite the greater number of patients with poorly differentiated HCCs, which is associated with an extremely high recurrence rate [31], the HAI group exhibited significantly better DFS than the non-HAI group. Furthermore, multivariate analysis revealed that the application of HAI is an independent favorable prognostic factor for DFS (Fig. 1a, Table 6). On the other hand, analysis of all patients revealed comparable extrahepatic recurrence rates in the two groups and that HAI was not a favorable prognostic factor for OS. Therefore, some systemic chemotherapy in addition to the HAI therapy might be required to reduce the risk of extrahepatic recurrence, ultimately increasing the OS. Because intrahepatic metastases after hepatic resection are reported to occur usually within 2 years postoperatively [32, 33] and PVTT often causes extensive intrahepatic metastasis of the tumor through the portal tract, the primary objective of adjuvant HAI is to reduce the risk of intrahepatic metastasis via the portal vein rather than multicentric recurrence [34]. Our results did not indicate any obvious differences between the two groups with respect to the recurrence rate within 2 years. However, the overall recurrence rate of the remnant liver in the HAI group was 31.5 %, which was significantly lower than the 68.5 % in the non-HAI group ($p = 0.001$).

In our analysis, the HAI group demonstrated significantly better DFS and OS than the non-HAI group in the limited Vp3/4 or Vv3 patients (Fig. 2) but not in the Vp2 or Vv2 patients. There is little information regarding recurrence or long-term survival with respect to the degree of tumor thrombi. Vp2 or Vv2 patients may not have widespread dissemination of tumor cells via the portal or hepatic vein. Furthermore, the extent of resected liver is limited, and the removal of tumor thrombi is easier and more complete than in Vp3/4 and Vv3 patients. In fact, operating time, blood loss, and the frequency of blood transfusion were significantly smaller in Vp2 and Vv2 patients (data not shown).

PVTT with multinodular or diffuse recurrence (i.e., intrahepatic dissemination) of HCC after thermal ablation is one of the most serious problems resulting in a poor

prognosis [10]. In this study, seven patients exhibited this recurrence pattern according to the histopathologic examinations of the resected specimens, and five patients underwent adjuvant HAI. The 5-year OS and DFS rates of these five patients were 80 % and 40 %, respectively, suggesting that hepatic resection followed by adjuvant HAI is also useful for PVTT with intrahepatic dissemination if the recurrence site is localized in the liver.

We applied mono- or bi-sectionectomy or (extended) hemi-hepatectomy in 42 (93.3 %) HCC patients with grade Vp2 or Vv2. Tumor thrombi might be completely removed by performing surgery alone in such cases. Among the nine patients with Vp3/4 (32.1 %), we applied the peeling-off technique for those with massive PVTTs beyond the bifurcation or into other sectors. This method is reported to have no disadvantages regarding curability compared to an en bloc technique [15]. The favorable 3-year DFS (32.4 %) and OS (58.3 %) rates of these nine patients may demonstrate the efficacy of the peeling-off technique for patients with grade Vp3/4.

Multivariate analysis revealed that adjuvant HAI was one of the independent favorable prognostic factors for DFS. However, the main limitation of this study is that it was not a randomized prospective study. Therefore, some confounders might have affected the results. The patients diagnosed with early recurrence (within 1 month) were analyzed as the non-HAI group because we aimed to investigate the advantages of adjuvant HAI in patients with resectable HCC and if HAI could be completed within 1 to 2 months. However, with the entry criteria used for the non-HAI group (early recurrence, advanced age, co-morbidities, poor performance), there is clearly a selection bias with less favorable prognostic factors in these patients.

Conclusions

Adjuvant HAI for HCC patients with macroscopic vascular invasion, especially patients with Vp3/4 or Vv3, might reduce the risk of recurrence without serious complications. However, a prospective randomized study is required to confirm our findings.

Conflict of interest The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Chemotherapy with bevacizumab for metastatic colorectal cancer: a retrospective review of 181 Japanese patients

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Abstract
Background There has so far been little information on the clinical effect of bevacizumab against colorectal cancer in Japan. Hence, this study was conducted to retrospectively evaluate the safety and efficacy of bevacizumab in clinical practice.
Methods A total of 181 patients with metastatic colorectal cancer (mCRC) received bevacizumab in combination with chemotherapy at 18 hospitals in Kumamoto prefecture, Japan. We surveyed the medical records of all patients regarding the patient characteristics, objective tumor responses, and adverse events. We analyzed their overall survival and the survival benefit when continuing the administration of bevacizumab beyond disease progression (progressive disease; PD) in patients who received bevacizumab-containing 1st line therapy.
Results The response rate (RR) in all lines of therapy was 42 %. The 1st line patients showed significantly better survival in comparison to the patients who received further lines of treatment ($P = 0.005$). There were no significant differences in survival between the group with post-PD treatment with bevacizumab and the group with post-PD treatment without bevacizumab ($P = 0.13$). The most common grade 3 or greater adverse event associated with bevacizumab was hypertension (12.2 %). Especially, a high incidence of gastrointestinal (GI) perforation was shown in this study (4.4 %) and most of the patients with GI perforation had some risk factors for this complication.
Conclusion Although the survival benefit of bevacizumab in Japanese patients with mCRC was similar to that observed in previous clinical trials, this study showed a high incidence of GI perforation in comparison to previous

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studies. Therefore, the careful selection of patients with few risk factors for this complication is likely to lead to a greater benefit from bevacizumab treatment.

Keywords Bevacizumab · Metastatic colorectal cancer · Target therapy

Introduction

Colorectal cancer is the second most common cancer and the third most common cause of death in Japan. Furthermore, its frequency is increasing in Japan [1, 2].

Prior to 2000, 5-fluorouracil (5-FU) plus leucovorin (LV) was the major chemotherapy regimen used to treat metastatic colorectal cancer (mCRC). Currently, oxaliplatin- or irinotecan-containing regimens are widely used and these regimens have increased the therapeutic options. Recently, the introduction of targeted therapies (such as bevacizumab, cetuximab, and panitumab) has dramatically changed the field of CRC therapy.

Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis, the altered regulation of which is associated with malignancy. VEGF has a crucial role in tumor growth, progression, and metastasis by promoting angiogenesis [3, 4]. Bevacizumab is a recombinant humanized monoclonal antibody to VEGF. Bevacizumab prevents the interaction of VEGF with receptors on vascular endothelial cells, and thereby abrogates VEGF receptor-mediated interacellular signaling and the resulting biological effects [5]. In addition to its direct antiangiogenic effect, bevacizumab may also improve the delivery of chemotherapy by altering the tumor vasculature and decreasing the elevated interstitial pressure in tumors [6, 7].

Bevacizumab significantly prolonged progression-free survival (PFS) [8, 9] and overall survival (OS) in phase III trials in patients with mCRC [8].

Bevacizumab was approved in Japan in June 2007. Only one Japanese clinical trial investigating the efficacy of bevacizumab has so far been reported [10]. However, in Japanese patients with mCRC, the evidence concerning the clinical efficacy and safety of bevacizumab is insufficient because of the limited experience. The purpose of this retrospective analysis was to evaluate the safety and efficacy of bevacizumab for Japanese patients with mCRC in clinical practice.

Patients and methods

Patients

The subjects included in this study were 181 patients with mCRC who received bevacizumab in combination with chemotherapy at 18 hospitals in Kumamoto prefecture, Japan, from June 2007 to December 2009. Two patients were lost to follow up. The mean observation period was 16.6 months. The eligible patients had histologically confirmed mCRC. The other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and adequate hematological, liver, and renal functions. Other assessments were carried out at the investigator's discretion. The patients described in this study were included in the findings of the nationwide post-marketing survey of bevacizumab in Japan.

Evaluation of the methods

Objective tumor responses were evaluated according to the response evaluation criteria in solid tumors version 1.0 (RECIST v1.0) by each attending doctor. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Statistical analyses were performed using the StatView5.0 software program (SAS Institute, Cary, NC, USA). The overall survival was calculated, using the Kaplan-Meier method, as the period from the date of bevacizumab treatment initiation until the date of death or until the last confirmed date of survival. The log-rank test was used to determine statistical significance. P values of <0.05 were considered to be significant.

Results

Table 1 shows the characteristics of the 181 enrolled patients. The median age of the patients was 62.6 years (range 24–83 years). A total of 102 patients were male and 79 patients were female. The most common sites of metastasis were the liver and lung.

There were 111/181 (61.3 %) patients for whom bevacizumab treatment was initiated as part of the 1st line regimen, and more than 90 % of the patients received bevacizumab in either the 1st line or 2nd line treatment. Table 2 shows the combination regimens used with bevacizumab. The majority of patients received an oxaliplatin-based combination regimen in the 1st line treatment, but in the patients with further lines of treatment, a greater number received an irinotecan-based combination regimen.

Table 3 shows the 2nd and 3rd line regimens used for patients treated with bevacizumab in the 1st line regimen. It was revealed that more than 60 % of the patients who were treated with bevacizumab in the 2nd line regimen had been receiving bevacizumab continuously. A new targeted therapy, cetuximab, was commonly initiated in the 3rd line treatment.

The objective tumor responses are summarized in Table 4. The response rate (RR) to the 1st line treatment was 51 %, while that in all treatment lines was 42 %, and the disease control rate (DCR) was 88 %. There were no responders in the 3rd and 4th line treatments, but 10 of the 12 patients receiving these treatments had stable disease.

Figure 1 shows the cumulative overall survival of all patients and the median survival time (MST), which was 23.0 months. The survival curves according to treatment line are compared in Fig. 1. The MSTs of the 1st line patients and the patients with further lines of treatment were 24.2 and 20.8 months, respectively. The 1st line patients showed significantly better survival in comparison to the latter patients ($P = 0.005$).

We analyzed the association of the survival benefit with the continuation of bevacizumab beyond disease progression (progressive disease; PD) in patients who received bevacizumab-containing 1st line therapy. We analyzed the association only for the 1st line patients. The median survival times of the patients who had post-PD treatment with bevacizumab and those who had post-PD treatment without bevacizumab were 25.5 and 18.6 months, respectively (Fig. 2). There were no significant differences in survival between the group who had post-PD treatment with bevacizumab and the group who had post-PD treatment without bevacizumab ($P = 0.13$). However, the group who had post-PD treatment with bevacizumab seemed to have a longer survival time than the group who had post-PD treatment without bevacizumab.

Table 1 Patient characteristics

Characteristics	Number of patients	(%)
Age (years)		
Median (range)	62.6	(24–83)
Sex		
Male	102	(56.4)
Female	79	(42.5)
Site of metastasis		
Liver	101	(55.8)
Lung	50	(27.6)
Lymph node	30	(16.6)
Peritoneum	24	(13.3)
Intrapelvic	10	(5.5)
Bone	9	(5.0)
Local recurrence	6	(1.7)
Line of treatment		
1st	110	(60.8)
2nd	58	(32.0)
3rd	9	(5.0)
≥4th	4	(2.2)
		($n = 81$)

Table 2 Combination regimens used with bevacizumab

Line of treatment	mFOLFOX6		FOLFOX4		FOLFIRI		FU/LV	
	Number of patients	(%)	Number of patients	(%)	Number of patients	(%)	Number of patients	(%)
1st line	87	(48.1)	16	(8.8)	7	(3.9)	1	(0.6)
2nd line	21	(11.6)	7	(3.9)	30	(1.7)	0	(0)
3rd line	2	(1.1)	1	(0.6)	6	(3.3)	0	(0)
≥4th line	1	(0.6)	0	(0)	1	(0.6)	1	(0.6)
Overall	111	(61.3)	24	(13.3)	44	(24.3)	2	(1.1)
		$n = 181$		$n = 181$		$n = 181$		$n = 181$

mFOLFOX6 modified FOLFOX6 (5-FU/leucovorin plus oxaliplatin), *FOLFOX4* 5-FU/leucovorin plus oxaliplatin, *FOLFIRI* 5-FU/leucovorin plus irinotecan, *FU/LV* fluorouracil/leucovorin

Table 3 The 2nd and 3rd line regimens used for patients who received bevacizumab as the 1st line treatment

Line of treatment	Regimen	Number of patients	(%)
2nd line		$n = 71$	
	Combination with bevacizumab	43	(61)
	Chemotherapy only	24	(34)
	Combination with cetuximab	4	(6)
3rd line		$n = 22$	
	Combination with bevacizumab	6	(27)
	Chemotherapy only	5	(23)
	Combination with cetuximab	11	(50)

Table 4 Objective tumor responses

Line of treatment	Clinical response				RR		DCR	
	CR	PR	SD	PD	Number of patients	(%)	Number of patients	(%)
1st line	1	45	37	7	46	51	83	92
2nd line	3	16	23	10	19	37	42	81
3rd line	0	0	7	2	0	0	7	75
≥4th line	0	0	3	0	0	0	3	100
Overall	4	61	70	19	65	42	135	88
						$n = 154$		$n = 154$

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* response rate, *DCR* disease control rate

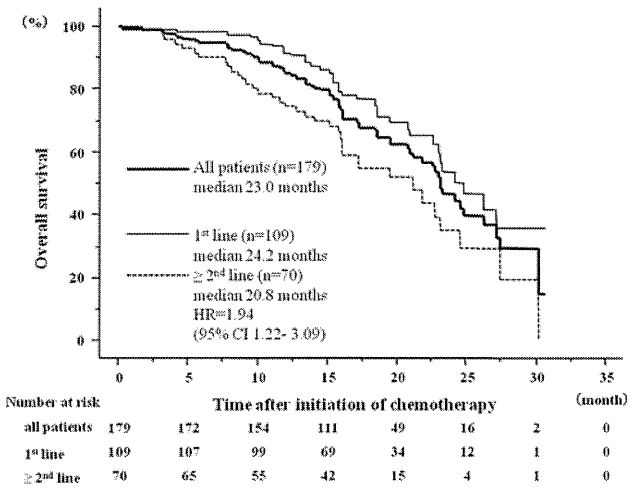

Fig. 1 **a** Cumulative overall survivals of all patients, patients with 1st line treatment, and patients with further lines of treatment. The median survival time of all patients was 23.0 months. *1st line* 1st line patients, *≥2nd line* patients with further lines of treatment. The median survival time was 24.2 months in the 1st line patients, compared with 20.8 months in the latter patients, corresponding to a hazard ratio (*HR*) for death of 1.94 ($P = 0.005$). The mean observation time was 16.6 months. *CI* confidence interval

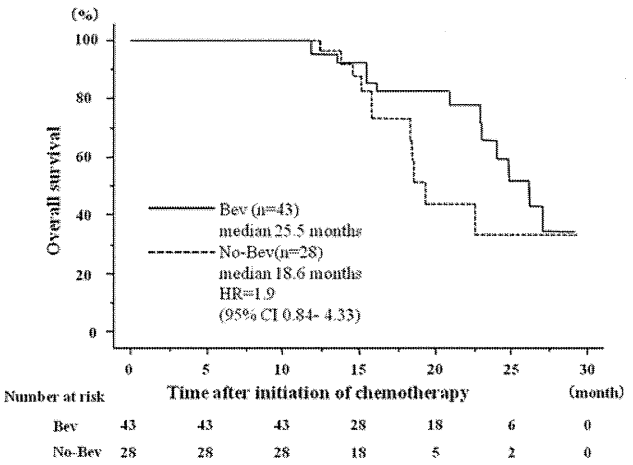

Fig. 2 Cumulative overall survivals in 71 patients with post-progressive disease (PD) treatment with or without bevacizumab. *Bev* post-PD treatment with bevacizumab, *No-Bev* post-PD treatment without bevacizumab. The median survival time was 25.5 months in the Bev group, compared with 18.6 months in the No-Bev group, corresponding to a hazard ratio (*HR*) for death of 1.9 ($P = 0.13$). The mean observation time was 18 months

Tables 5 and 6 list grade 3 or greater hematological and non-hematological adverse events. The incidences of grade 3 or greater adverse events were as follows: neuropathy occurred in 33 patients (18.2 %), neutropenia in 31 patients (17.1 %), anorexia in 28 patients (15.5 %), nausea/vomiting in 26 patients (14.4 %), hypertension and diarrhea/constipation in 22 patients (12.2 %), fatigue in 18 patients (9.9 %), thrombocytopenia in 10 patients (5.5 %), coagulation abnormalities in 2 patients (1.1 %), and ischemic heart disease in 1 patient (0.6 %). Hypertension, bleeding, proteinuria, venous/arterial thrombosis, gastrointestinal (GI) perforation, wound-healing complications, and allergic reactions have often been reported as bevacizumab-related adverse events [11–14]. In our cohort, cytotoxic chemotherapy-related adverse events, such as neuropathy and neutropenia, constituted the majority of the adverse events. The most common grade 3 or greater adverse event associated with bevacizumab was hypertension. It is noteworthy that GI perforation occurred at a relatively high frequency, in 8 of the 181 patients (4.4 %). Table 7 shows the characteristics of the patients with GI perforation. The mean period from the initiation of bevacizumab to GI perforation was 25.3 days. The GI perforation occurred at the tumor site in two patients, in the colon in two patients with primary resection, and in the small intestine in the other four patients. In addition, 2 of these 8 patients had a history of abdominal/pelvic radiotherapy, 1 had had a Meckel diverticulum resection, and 3 had a history of peritoneal carcinomatosis.

Discussion

Combinations of bevacizumab with chemotherapy have shown increased efficacy compared with chemotherapy

Table 5 Grade 3 or greater hematological adverse events

Adverse event	1st Line		Overall	
	Number of patients	(%)	Number of patients	(%)
Neutropenia	18	9.9	31	17.1
Thrombocytopenia	4	2.2	10	5.5
Leukopenia	2	1.1	5	2.8
Coagulation abnormality	0	0	2	1.1

Table 6 Grade 3 or greater non-hematological adverse events

Adverse event	1st Line		Overall	
	Number of patients	(%)	Number of patients	(%)
Neuropathy	20	11.0	33	18.2
Anorexia	17	9.4	28	15.5
Nausea/vomiting	13	7.2	26	14.4
Diarrhea/constipation	10	5.5	22	12.2
Fatigue	12	6.6	18	9.9
Oral ulcer	11	6.1	15	8.3
Alopecia	8	4.4	11	6.1
Dysgeusia	5	2.8	6	3.3
Rash	3	1.7	5	2.8
Liver dysfunction	0	0	2	1.1
Fever elevation	0	0	2	1.1
Ischemic heart disease	1	0.6	1	0.6
Hypertension	12	6.6	22	12.2
GI perforation	5	2.8	8	4.4
Hemorrhage	4	2.2	8	4.4
Allergic reaction	0	0	4	2.2
Thrombosis	2	1.1	2	1.1
Wound-healing complication	1	0.6	1	0.6
Proteinuria	1	0.6	1	0.6
Other	1	0.6	4	2.2

Table 7 Characteristics of patients with gastrointestinal (GI) perforation

Case no.	Treatment line	Period from the initiation of bevacizumab to GI perforation (days)	Perforation site and details
Case 1	1	40	Tumor site, peritoneal carcinomatosis
Case 2	3	13	Tumor site
Case 3	1	27	Small intestine, peritoneal carcinomatosis
Case 4	1	6	Colon (primary resection), peritoneal carcinomatosis
Case 5	2	8	Colon (primary resection), abdominal/pelvic radiotherapy
Case 6	1	55	Small intestine, abdominal/pelvic radiotherapy
Case 7	1	28	Small intestine
Case 8	1	Not known	Small intestine, Meckel diverticulum resection