Table 7 Late toxicities: heart disease

Characteristics	*n*	Heart disease	
		n (%)	*p* value
Age (years)			
≤70	49	5 (10)	n.s.
>70	38	6 (16)	
Gender			
Male	80	9 (11)	n.s.
Female	7	2 (29)	
KPS			
90–100	71	7 (10)	n.s.
60–80	16	4 (25)	
Operability			
Operable	33	2 (6)	n.s.
Inoperable	54	9 (17)	
Tumor depth			
Mucosal	44	6 (14)	n.s.
Submucosal	43	5 (12)	
Tumor length (cm)			
≤3.0	63	7 (11)	n.s.
>3.0	24	4 (17)	
Treatment			
IBT alone	27	2 (7)	n.s.
IBT + EBRT	60	9 (15)	
Diabetes mellitus			
Yes	14	2 (14)	n.s.
No	73	9 (12)	
Heart disease history			
Yes	14	6 (43)	0.002
No	73	5 (7)	
Hypertension			
Yes	15	2 (13)	n.s.
No	72	9 (13)	
Alcoholic drinking			
Yes	64	7 (11)	n.s.
No	23	4 (17)	
Tobacco smoking			
Yes	66	7 (11)	n.s.
No	21	4 (19)	

KPS Karnofsky performance status, *n.s.* not significant

occurred in patients treated with IBT fractional doses of 2.0 and 2.5 Gy. We need to be aware of the occurrence of severe esophageal ulcer even when we perform IBT with a low fractional dose.

In our study, Grade ≥3 pneumonitis, pleural effusion and pericardial effusion developed in 0, 0 and one patient, respectively. This result suggests that RT without chemotherapy was safe regarding these toxicities. We also investigated cardiac ischemia and heart failure after treatment. Nine patients suffered Grade ≥3 events. Two died of AMI and one died of heart failure. Five of them had a history of heart disease, and a history of heart disease was the only significant factor associated with developing events of cardiac ischemia and heart failure after RT ($p = 0.002$). Radiation-induced heart disease is one of the complications after thoracic RT. The effects on various portions of heart, such as pericardium, myocardium or coronary artery, due to RT have been reported [27–29]. In CRT of esophageal cancer, cardiopulmonary toxicities became problems to be solved after the report by Ishikura et al. [30]. We are not sure whether all events of cardiac ischemia and heart failure in this study occurred due to irradiation. However, in the RT for esophageal cancer, irradiation to the heart cannot be avoided. Therefore, efforts should be made to decrease the irradiation dose to the heart as much as possible using the newest technique. Furthermore, follow-up with attention to development of heart disease is important.

As mentioned previously, the role of IBT has been limited in the treatment of SEC. However, we consider that IBT can be a treatment option for mucosal cancer patients who have multiple or large legions that have a risk of severe esophageal stenosis by endoscopic resection and for submucosal cancer patients who have difficulties in receiving surgery or concurrent chemotherapy because of high age or concurrent illnesses.

In conclusion, there was a clear difference in treatment results depending on tumor depth. The outcomes of IBT combined with EBRT for submucosal cancer were not satisfactory and more intensive treatment should be considered. In our institution, CRT was introduced for submucosal cancer after 2002 and the efficacy and safety of CRT are currently under investigation.

Conflict of interest No author has any conflict of interest.

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Cancer Chemother Pharmacol (2012) 69:1499–1505
DOI 10.1007/s00280-012-1853-7

ORIGINAL ARTICLE

Neoadjuvant chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil for esophageal cancer

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Received: 27 January 2012 / Accepted: 14 February 2012 / Published online: 2 March 2012

Abstract
Purpose We aimed to evaluate the safety, tolerability, and efficacy of combination preoperative chemoradiotherapy as first-line treatment in patients with advanced esophageal cancer.
Methods We performed a phase I dose-escalation trial of docetaxel at 25–40 mg/m^2 in four planned dose levels in 3–6 patient cohorts on days 1, 15, 29, and 43 administered in combination with cisplatin (70 mg/m^2 on days 1 and 29) and 5-fluorouracil (70 mg/m^2/day on days 1–4 and 29–32) and concurrent radiation therapy (40 Gy). The tumors were resected during weeks 10–13.
Results This study included 7 patients with esophageal cancer. The dose-limiting toxicity was observed at a biweekly docetaxel dose of 30 mg/m^2 when patients developed grade 3 febrile neutropenia, grade 4 thrombocytopenia, and grade 4 pain/esophagus, resulting in a maximum tolerated dose of 25 mg/m^2. Grade 3/4 hematological toxicity was observed in 71% of the patients and grade 3/4 non-hematological toxicity in 57%. The overall tumor response rate was 86% (complete, 57% and partial, 29%). All patients underwent surgery, and there were no deaths as a result of postoperative complications.
Conclusions This preoperative chemoradiotherapy regimen using triplets is feasible but results in moderate toxicity. It is noteworthy that this regimen was associated with a high rate of pathological complete remission.

Keywords Esophageal cancer · Chemoradiotherapy · Docetaxel · Cisplatin · 5-Fluorouracil

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Introduction

Esophageal cancer is the sixth leading cause of cancer deaths in Japanese men. An estimated 12,000 individuals die due to esophageal cancer every year [1]. The incidence of esophageal adenocarcinomas is increasing in Western Europe and the United States, whereas esophageal squamous cell carcinomas are the most commonly encountered type of esophageal cancer in Japan. Most patients with newly diagnosed carcinoma of the esophagus present with locally advanced disease. Since the incidence of locoregional and distant failure is high, considerable interest has been generated in combining local and systemic therapy. Preoperative chemoradiotherapy and surgery are potentially curative for patients with locoregional disease, and this treatment is probably superior to surgery alone [2–4]. However, prognosis for these patients remains poor. In an effort to improve treatment results, newer combinations of chemotherapy with radiotherapy have been evaluated.

5-Fluorouracil and cisplatin (CF) are the most commonly used agents in combination chemotherapy and radiotherapy. A V325 phase III study on gastric cancer demonstrated that adding docetaxel to CF significantly improved the time to progression, survival, and overall response rate as compared to treatment with CF alone [5]. A randomized trial of squamous cell carcinoma of the head and neck illustrated the advantages of combining docetaxel, cisplatin, and 5-fluorouracil as induction

chemotherapy compared to cisplatin and 5-fluorouracil, when followed by chemoradiotherapy [6]. On the basis of these studies, it was hypothesized that a preoperative therapy consisting of a chemotherapy combining docetaxel, cisplatin, and 5-fluorouracil, followed by radiotherapy, could significantly improve the prognosis of patients with localized esophageal cancer. The present work is a phase I clinical trial designed to evaluate the safety and efficacy of this neoadjuvant chemotherapy. The primary end point was dose-limiting toxicity (DLT) during chemoradiation. Secondary objectives were feasibility and efficacy of the neoadjuvant chemoradiotherapy.

Methods

Eligibility

Previously untreated patients with histological proof of squamous cell carcinoma of the thoracic esophagus or gastroesophageal junction (GEJ), with clinical T2–T3 N0–3, and M0 (including supraclavicular or celiac lymph node involvement) disease according to the American Joint Committee on Cancer (AJCC), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 were eligible to participate in this study.

The patients were required to have measurable disease by radiological or endoscopic evaluation at the time of enrollment. Other eligibility criteria included age $\leq$75 years, adequate organ function (white blood cell count [WBC], $\geq$3,000/μL; platelet count, $\geq$100 $\times$ 109/L; serum bilirubin, $\leq$1.5 $\times$ the upper limit of normal (UNL); serum, AST/ALT less than 1.5 $\times$ the UNL; alkaline phosphatase, <2.5 $\times$ the UNL; and serum creatinine, $\leq$1.2 mg/dL; or calculated creatinine clearance, $\leq$60 mL/min). The exclusion criteria included history of hypersensitivity to docetaxel, cisplatin (CDDP), 5-fluorouracil (5-FU), or polysorbate 80; infection with fever elevation; peripheral neuropathy >grade 1; any other serious preexisting medical illnesses; pregnancy or lactation; and prior invasive malignancy within 5 years. This study was approved by the Institutional Ethics Committee, and all the patients provided their written informed consents prior to the enrollment.

Treatment plan

Radiation therapy

External beam radiotherapy was given at 5 fractions per week for 4 weeks (total dose, 40 Gy) [7]. Radiotherapy was delivered using 10-MV X-rays. A computed tomography (CT) simulator was used for three-dimensional treatment planning. The radiation field for upper thoracic tumors included the region from the supraclavicular, cervical, and mediastinal lymph nodes to the carina. The field for mid-thoracic or lower thoracic tumors included the cervical, mediastinal, and perigastric lymph nodes, and the supraclavicular fossa was included if the cervical nodes tested positive. The field for GEJ tumors included the mediastinal (lower than subcarinal), perigastric, and celiac lymph nodes. The primary tumor was included with a craniocaudal margin of 2–3 cm.

Concurrent chemotherapy

During radiotherapy, all patients received intravenous docetaxel (days 1, 15, 29, and 43), CDDP (days 1 and 29), and 5-fluorouracil (days 1 thorough 4 and days 29–32), as shown in Fig. 1. Initial dose levels were influenced by dose levels reported as a phase I trial of definitive chemoradiotherapy by Higuchi et al. [8]. They used docetaxel (20–40 mg/m^2) and an infusion of cisplatin (40 mg/m^2) on day 1 plus a continuous infusion of 5-fluorouracil (400 mg/m^2/day) on days 1–5, administered every other week and recommend the following dosage for phase II studies of DCF plus radiotherapy: docetaxel 35 mg/m^2, cisplatin 40 mg/m^2, and 5-fluorouracil 400 mg/m^2/day with 61.2 Gy of concurrent radiotherapy. We reduced the dose with respect to neoadjuvant chemoradiotherapy. We used a conventional dose-escalation schema with the primary end point of defining the DLT of docetaxel that can be delivered with CDDP, 5-fluorouracil, and radiotherapy, as shown in Table 1. Steroids and antiemetic premedication were administered to all the patients.

Definition of dose-limiting toxicities (DLTs): The following toxicities (according to the Common Terminology Criteria for Adverse Events (version 3.0) of the National Cancer Institute) that occurred during chemoradiotherapy or before surgery were defined prospectively as DLTs:

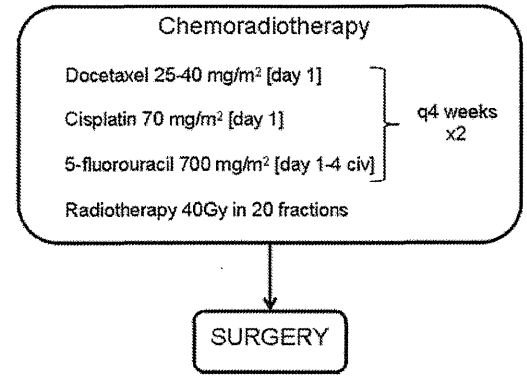

Fig. 1 A schematic showing the treatment and the dosage of different drugs

Table 1 Chemotherapy dose levels

	Docetaxel (mg/m^2) Day 1, 15	Cisplatin (mg/m^2) Day 1	5-FU (mg/m^2/day) Days 1–4
Level 1	25	70	700
Level 2	30	70	700
Level 3	35	70	700
Level 4	40	70	700

(1) grade 4 neutropenia or leucopenia (persisting for 5 days or longer); (2) grade 4 thrombocytopenia; (3) grade 3 or 4 febrile neutropenia; (4) other grade 3 or 4 non-hematological toxicity, except for grade 3 esophagitis, nausea, vomiting, anorexia, and diarrhea within 3 days, dyspepsia, hyperglycemia, and abnormalities of sodium, potassium, and calcium; (5) omission of chemotherapy >1 week; (6) interruption of radiotherapy for >1 week.

Dose-escalation schema

At least three patients were enrolled at each level. If no DLT was observed, the next dose level was opened for enrollment. If DLT was observed in one or two patients, then up to three additional patients were enrolled. Intrapatient dose escalation was not permitted. If 3 or more patients experienced DLTs, the dose escalation was stopped and that dose was regarded as the maximum tolerated dose (MTD). The recommended dose (RD) for the phase II study of docetaxel was determined to be one dose level below the MTD.

Suspended criteria of chemoradiotherapy: In the case of toxicity, no dose modification was allowed in this study. If hematological toxicity ≥grade 3 occurred, administration of the chemotherapy was delayed until the platelet count was $\geq 10 \times 10^4/mm^3$, and absolute neutrophils were $\geq 2 \times 10^3$. Radiotherapy continued despite chemotherapy interruptions. Radiotherapy, together with chemotherapy, was suspended if the patient experienced grade 4 esophagitis until improvement to grade 2.

Surgery

Patients were underwent definitive surgical resection from weeks 10–13. The patients in whom the primary tumor was located in the upper or middle thoracic esophagus underwent transthoracic esophagectomy (involving laparotomy, right thoracotomy, and cervical anastomosis) with three-field lymph node dissection (thoracic, abdominal, and cervical). Those whose primary tumor was located in the lower thoracic or abdominal esophagus underwent transthoracic esophagectomy with two-field lymph node dissection. Reconstruction was usually carried out via a gastric tube through the posterior mediastinal or retrosternal route.

Definition of response

The tumors, nodes, and metastases were staged according to the International Union against Cancer criteria [9]. Clinical staging was carried out using results of endoscopy, endoscopic ultrasound, barium swallow, computed tomography scanning of the abdomen and thorax, and positron-emission tomography.

The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate the responses in all the patients. The final response category assigned to the patients represented the best response obtained during treatment. All the patients were reassigned into stages 3–4 weeks after completing combined therapy (week 9) using results of CT scans, endoscopy and, where available, endoscopic ultrasound and positron-emission tomography. Histopathological response, a secondary end point, was based on the pathological findings after esophagectomy. Pathological complete remission (pCR) was defined as the complete disappearance of the tumor on histological examination.

Monitoring procedures and follow-up

During treatment, patients were reviewed weekly, and their weight, patient performance status (PS), and physical examination were measured, and acute toxicities were recorded. Biochemical analysis and creatinine clearance were measured weekly from blood samples obtained from the patients every week.

After active treatment, the patients were examined (including CT scan) every 3 months for the first year, every 4 months in the next year, and then every 6 months in the next 3 years. Endoscopic examination was carried out annually.

Results

Patients

Between December 2009 and November 2010, we enrolled 7 patients with esophageal cancer into this study. Patient characteristics are summarized in Table 2. There were 5 male and 2 female subjects of ages ranging from 38 to 71 years (median, 61 years). The PS was 0 in all cases. Of these, 5 patients had stage IIIA esophageal cancer and 2 had stage IIIB esophageal cancer. All the patients had squamous cell carcinoma.

Table 2 Patient characteristics

Age (year)	
Median	61
Range	38–71
Gender (*n*, %)	
Male	5 (71.4)
Female	2 (28.6)
ECOG performance (*n*, %)	
0	6 (85.7)
1	1 (14.3)
AJCC TNM stage (*n*, %)	
IIIA	5 (71.4)
IIIB	2 (28.6)
Histological type (*n*, %)	
Squamous cell	7 (100)

ECOG Eastern Cooperative Oncology Group, *AJCC* American Joint Committee on Cancer

Treatment delivery and toxicity

All the patients were evaluated for toxicity weekly during radiotherapy and concurrent chemotherapy. The adverse effects of the treatment are summarized in Table 3. The patients completed planned radiotherapy without any treatment interruptions. Hospitalization and intravenous fluids were required in the case of 4 patients with grade 3 esophagitis.

Among the 3 patients who were administered level 1 docetaxel, none had DLTs. Of the 3 patients who were administered level 2 docetaxel, 2 had DLT. One patient in dose level 2 experienced grade 3 febrile neutropenia. This event caused a delay in chemotherapy; however, radiotherapy was completed without any interruption. Despite the use of opioids, 1 patient at dose level 2 experienced severe pain due to esophagitis after the completion of radiotherapy. Since the pain resulted in the patient becoming confined to bed, we deemed it as grade 4 pain and DLT. However, these symptoms disappeared after approximately 2 weeks of central venous nutrition. Therefore, a fourth patient was treated. This additional patient had grade 4 thrombocytopenia. Therefore, DLT occurred in 3 of the 4 patients, and the level 2 dose was designated as the MTD and the level 1 dose was designated as the RD for phase II studies. One patient who was administered level 2 docetaxel had grade 4 hyponatremia and was diagnosed with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), but this patient recovered after water restriction, and Na supplements were applied.

All the patients underwent definitive surgical resection during weeks 10–13. Four patients underwent transthoracic esophagectomy with three-field lymph node dissection and 3 underwent transthoracic esophagectomy with two-field lymph node dissection. Infections were the predominant complication of surgery (Table 4) and occurred in 3 patients (43%). One patient (14%) developed anastomotic leakage, which was resolved with conservative measures. There were no deaths at 30 days after the surgery. Furthermore, there was no in-hospital mortality during the 6-month follow-up, and there were no treatment-related deaths.

Response

All the 7 patients are included in the response analyses (Table 5). Complete pathological response was seen in 3 patients and partial response in 4 patients with an overall response rate of 86%. One patient had progressive disease. Complete tumor resection with microscopically clear

Table 3 Common toxicities (NCI-CTC version 3)

	Level 1 ($n = 3$)			Level 2 ($n = 4$)			Overall ($n = 7$)		
	Any	G3	G4	Any	G3	G4	Any	G3	G4
Leukopenia	3	2	0	4	3	0	7	5	0
Neutropenia	3	1	0	4	3	0	7	4	0
Anemia	3	0	0	4	1	0	7	1	0
Thrombocytopenia	1	0	0	2	1	1[a]	3	1	1
Febrile neutropenia	0	0	0	1	1[a]	0	1	1	0
Creatinine	1	0	0	1	0	0	2	0	0
Anorexia	3	1	0	4	0	0	7	1	0
Nausea	3	0	0	4	0	0	7	0	0
Vomiting	0	0	0	0	0	0	0	0	0
Esophagitis	3	2	0	4	2	0	7	4	0
Pain/esophagus	3	2	0	3	1	1[a]	6	3	1
Diarrhea	1	0	0	0	0	0	1	0	0
Fatigue	3	0	0	2	1	0	5	1	0

[a] Three patients in dose level 2 experienced dose-limiting toxicity

Table 4 Post-operative complications (within 30 days of surgery) in patients undergoing resection

Complications	Thoracic surgery ($n = 7$)
Postoperative infection	2
Anastomotic leakage	1
Anastomotic stricture	1
Recurrent nerve paralysis	2
Recurrent nerve paralysis	3
Pneumonia	1
Re-operation	0

Anastomotic leakage: The condition resolved with conservative treatment

There were no deaths as a result of postoperative complications during the study

margins (R0 resection) was achieved in 6 of the 7 patients (86%).

Discussion

Gebski et al. [10] conducted a recent meta-analysis of neoadjuvant chemoradiotherapy for resectable esophageal cancer; they reported that a significant survival benefit was evident for preoperative chemoradiotherapy and suggested that evidence-based treatment be used for esophageal cancer. Tepper et al. [4] used chemotherapeutic agents—100 mg/m^2 cisplatin and 1,000 mg/m^2/for 4 days 5-fluorouracil with radiotherapy (50.4 Gy total dose)—and reported favorable results for neoadjuvant chemoradiation followed by surgery. In particular, the 5-year survival was 16% (95% CI, 5–33%) in the surgery-alone group versus 36% (95% CI, 21–57%) in the neoadjuvant chemoradiation group. In addition, the use of neoadjuvant chemoradiation did not appear to increase operative mortality, and the preoperative therapy was associated with manageable toxicity.

Because the achievement of pCR in the primary tumor after preoperative CRT is a positive long-term outcome [11, 12], regimens of new drug combinations containing docetaxel, paclitaxel, and/or other molecular target agents have been tested to achieve higher rates of pCR and improve survival benefit of preoperative chemoradiation for resectable esophageal cancer [13].

In this study, to improve the therapeutic effect of standard cisplatin plus 5-FU concurrent chemoradiotherapy, we focused on docetaxel incorporation into the therapy, which has been extensively used with radiation for the treatment of patients with non-small lung cancer and head and neck cancer [14, 15]. Although not powered to demonstrate improvements in cancer outcomes, this study shows that the addition of docetaxel to the current preoperative chemotherapy plans combining cisplatin and 5-FU provides a high response rate. Pathological CR rate of 43% compares favorably with other chemoradiotherapy studies using cisplatin and 5-FU [3, 4].

Esophagitis was the most frequent toxicity in this study. Hospitalization was required in 2 of 3 level 1 patients and 2 of 4 level 2 patients who experienced grade 3 esophagitis.

Spigel et al. [16] used a triplet regimen consisting of oxaliplatin, docetaxel, and capecitabine in combination with radiation therapy. Grade 3 esophagitis occurred in 20% of all cases. Day et al. [17] conducted a phase I trial of cisplatin and docetaxel concurrent with 50 Gy radiotherapy. In this trial, grade 3 radiation esophagitis was found to be the most common acute toxicity (37.5%). In our study, regional lymph nodes were included in the clinical target volume (CTV) as a prophylactic irradiation field for patients with no clinical evidence of lymph nodes metastases, which was larger than the irradiation field used in previous trials. This increased irradiation field could be attributed to the occurrence of esophagitis, which was the most commonly encountered adverse event.

In radiotherapy, there is no clear consensus about the CTV, especially regarding inclusion of regional lymph nodes in the CTV when there is no clinical evidence of lymph node metastases of esophageal cancer.

A recent publication has suggested that the 5-year survival improves with the number of lymph nodes removed and that this effect is observed for the removal of over 40

Table 5 Histopathological response and clinical course

Patient no.	Dose level	Stage	Clinical response		Pathological response		Status (month)
			Primary	LN	Primary	LN	
1	1	IIIB (T3N2)	PR	PR	CR	CR	ADF (18)
2	1	IIIA (T3N1)	PR	PR	PR	CR	AWD (17)
3	1	IIIB (T3N2)	PR	PR	CR	PR	ADF (17)
4	2	IIIA (T3N1)	CR	CR	CR	CR	ADF (14)
5	2	IIIA (T3N1)	CR	CR	CR	PR	ADF (11)
6	2	IIIA (T3N1)	PD	NC	PD	NC	AWD (10)
7	2	IIIA (T3N1)	CR	PR	CR	CR	ADF (6)

AWD alive with disease, *ADF* alive and disease free, *CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease

nodes [18]. Another study showed that the total number of surgically resected lymph nodes is independently associated with the overall and disease-free survival in esophageal cancer [19, 20]. We believe that neoadjuvant chemoradiotherapy aims to resect not only primary tumors but also lymph nodes and surrounding tissues with microscopically clear margins that may be potentially involved, and neoadjuvant chemoradiotherapy is associated with improved lymphadenectomy. Therefore, regional lymph nodes were included as a prophylactic irradiation field in the CTV.

In this trial, the 3 agents—docetaxel, cisplatin, and 5-fluorouracil—were found to be well tolerated when combined with radiation in patients with potentially resectable esophageal cancer. The antitumor efficacy, as demonstrated by the high pathological response rate, was also extremely encouraging. Moreover, it is noteworthy that there was no indication of increased operative mortality and morbidity in our trial.

A phase II study in esophageal cancer using the doses found in this study (25 mg/m^2 docetaxel on days 1, 15, 29, and 43; 70 mg/m^2 cisplatin on days 1 and 29; 700 mg/m^2/day 5-FU on days 1–4 and 29–32; and 40 Gy radiotherapy) is currently underway at our institution.

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Hepatology Research

Hepatology Research 2012; 42: 442–453 doi: 10.1111/j.1872-034X.2011.00943.x

Original Article

Hepatic arterial infusion chemotherapy using 5-fluorouracil and systemic interferon-α for advanced hepatocellular carcinoma in combination with or without three-dimensional conformal radiotherapy to venous tumor thrombosis in hepatic vein or inferior vena cava

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Aim: We investigated the efficacy of hepatic arterial infusion chemotherapy (HAIC) using 5-fluorouracil (5-FU) and systemic interferon (IFN)-α (HAIC-5-FU/IFN) for advanced hepatocellular carcinoma (HCC) with venous tumor thrombosis (VTT) in the hepatic vein trunk (Vv2) or inferior vena cava (Vv3).

Methods: Thirty-three patients with HCC/Vv2/3 underwent HAIC with 5-FU (500 mg/body weight/day, into hepatic artery on days 1–5 on the first and second weeks) and IFN-α (recombinant IFN-α-2b 3 000 000 U or natural IFN-α 5 000 000 U, intramuscularly on days 1, 3 and 5 of each week). Three-dimensional conformal radiotherapy (3D-CRT) was used in combination with HAIC-5-FU/IFN in 14 of 33 patients to reduce VTT.

Result: The median survival time (MST) was 7.9 months, and 1- and 2-year survival rates were 30% and 20%, respectively. Evaluation of intrahepatic response after two cycles of HAIC-5-FU/IFN showed complete response (CR) in three (9%) and partial response (PR) in seven (21%), with an objective response rate of 30%. Multivariate analysis identified reduction of VTT ($P = 0.0006$), size of largest tumor ($P = 0.013$) and intrahepatic response CR/PR ($P = 0.030$) as determinants of survival. CR/PR correlated significantly with tumor liver occupying rate ($P = 0.016$) and hepatitis C virus Ab ($P = 0.010$). Reduction of VTT correlated significantly with radiotherapy ($P = 0.021$) and platelet count ($P = 0.015$). Radiotherapy-related reduction in VTT significantly improved survival of 16 patients with Vv3 and non-CR/PR response of HAIC-5-FU/IFN ($P = 0.028$).

Conclusion: As for advanced HCC with VTT of Vv2/3, HAIC-5-FU/IFN responsive patients could obtain favorable survival. Despite ineffective HAIC-5-FU/IFN, the combination with effective radiotherapy to VTT might improve patients' prognosis.

Key words: 5-fluorouracil, hepatocellular carcinoma, interferon, radiotherapy, venous tumor thrombosis

INTRODUCTION

THE PROGNOSIS OF patients with advanced hepatocellular carcinoma (HCC) remains poor,[1–3] although that of patients with HCC has gradually improved following the development of new diagnostic techniques and advancements in therapeutic modalities, such as surgical resection, radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), radiotherapy and hepatic arterial infusion chemotherapy (HAIC).[4–8] Recent advances in implantable drug delivery systems have facilitated repeated arterial infusions of anti-cancer agents to tumors in the corresponding arterial perfusion area. HAIC is considered suitable for HCC patients with poor hepatic reserve due to high drug concentrations in

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Received 8 June 2011; revision 19 October 2011; accepted 9 November 2011.

local tissue and late rates of adverse effects of anti-cancer agents. Among several anti-cancer agents, intra-arterial 5-fluorouracil (5-FU) and systemic interferon (IFN) have been reported as one of the most effective combination chemotherapies for HCC with portal vein tumor thrombus (PVTT).[9–13] Vascular invasion of HCC with PVTT, venous tumor thrombosis (VTT) and biliary thrombosis in the liver, represent the worst prognostic factors in patients with advanced HCC, especially PVTT.[14–19] On the other hand, VTT is less commonly recognized poor prognostic factor than PVTT. To define the therapeutic benefits of HAIC-5-FU/IFN for HCC with VTT in the hepatic vein trunk (Vv2), or inferior vena cava (Vv3), we retrospectively analyzed the treatment response, survival time and prognostic factors.

Three-dimensional conformal radiotherapy (3D-CRT) allows the delivery of higher radiation doses to tumors and low radiation dose to normal tissue. 3D-CRT improves the anti-tumor effect of radiotherapy and minimizes damage to normal tissue. This modality is probably suited as local radiotherapy for PVTT in patients with poor hepatic reserves.[20,21] The synergistic effects of the combination of chemotherapy and radiotherapy have been reported in various malignancies such as lung cancer and esophageal cancer.[22–25] Recently, Han *et al.*[26] reported a response rate of 45% in HCC patients with PVTT treated by HAIC with 5-FU/cisplatin and 3D-CRT. Furthermore, Katamura *et al.*[27] reported the efficacy of intra-arterial 5-FU/IFN combined with 3D-CRT for PVTT. To our knowledge, there are no studies on the therapeutic efficacy of radiotherapy for HCC with VTT. In addition, it is still unclear whether radiotherapy has any additional effects on HAIC-5-FU/IFN. Based on the above results, we retrospectively analyzed and compared differences in the clinical course and outcome of HCC patients treated by HAIC-5-FU/IFN with or without 3D-CRT.

METHODS

Study design and eligibility

THE FOLLOWING ENROLLMENT criteria were applied in the study: (i) HCC with VTT in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein (Vv2), or inferior vena cava (Vv3); (ii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or PS 1; (iii) Child–Pugh stage A or B; (iv) serum total bilirubin <3.0 mg/dL; (v) leukocyte count >2000/mm^3; (vi) platelet count >50 000/mm^3; (vii) serum creatinine <1.5 mg/dL; (viii) at least a 4-week rest period of no treatment since any previous treatment for HCC; (ix) the initial administration of HAIC for HCC; and (x) no other serious medical condition that would interfere with HAIC. The presence of extrahepatic metastases was not an exclusion criterion when they were not considered prognostic factors. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Hiroshima University. Written informed consent was obtained from each patient after detailed explanation about the therapy. From March 2004 to November 2010, 33 patients met the above criteria for HAIC-5-FU/IFN. The baseline characteristics of these patients are summarized in Table 1.

Treatment protocol

The patients received repeated arterial infusion chemotherapy via drug delivery systems implanted in the subcutaneous inguinal region. The arterial catheter was implanted using the method described previously by our group.[9] One course of chemotherapy represented 2 weeks. 5-FU (500 mg/body weight/day; Kyowa Hakko, Tokyo) was administered using a mechanical infusion pump from day 1 to day 5 on the first and second weeks. Recombinant IFN-α-2b (Intron A, Schering-Plough Pharmaceuticals, Osaka, Japan) at 3 000 000 U (3 MU) or natural IFN-α (OIF, Otsuka Pharmaceuticals, Tokyo) at 5 000 000 U (5 MU), was administered intramuscularly on days 1, 3 and 5 of each week (total dose: 18 and 30 MU, respectively). As for the two types of IFN, similar effects were reported previously between recombinant IFN-α-2b and natural IFN-α when combined with intra-arterial 5-FU for the treatment of advanced HCC.[10] After each treatment course, 2–4 weeks of rest/no treatment period was enforced. HAIC-5-FU/IFN was repeated several times during the treatment as much as possible, until we considered that it was impossible to continue further HAIC-5-FU/IFN based on the following criteria: (i) PS changed to 3 or 4; (ii) adverse events were estimated as grade 4 by Common Technology Criteria for Adverse Events (CTCAE) version 4.0; (iii) patients were evaluated clinically to have progressive disease; and (iv) patient requested termination of treatment. Fourteen out of 33 patients received 3D-CRT to VTT to control VTT progression. 3D-CRT was applied to objective progressive VTT of Vv2/3, which was shown in dynamic computed tomography (CT) before or during two courses of HAIC-5-FU/IFN. From March 2004 to July 2006, when the decision to introduce 3D-CRT was clinically left to the

Table 1 Clinical characteristics of 33 patients with hepatocellular carcinoma (HCC) and venous tumor thrombus (VTT)

Clinical characteristics	Category	
Sex	Male/female	30/3
Age	<65 years/≥65 years	15/18
ECOG PS	0/1	23/10
HCV Ab	+/−	16/17
HBs Ag	+/−	7/26
Child–Pugh stage	A/B	25/8
Previous treatment	Yes/no	9/24
α-fetoprotein (ng/mL)	<5 000/≥5 000	17/16
des-γ-carboxy prothrombin (mAU/mL)	<10 000/≥10 000	14/19
Platelet count (/mm^3)	<150 000/≥150 000	19/14
Size of largest tumor (mm)	<100/≥100	16/17
Tumor liver occupying rate (%)	<50/≥50	20/13
Tumor stage†	IVA/IVB	19/14
Grade of venous invasion‡	Vv 2/3	13/20
Grade of portal invasion§	Vp 0/1/2/3/4	7/1/4/8/13
Extrahepatic metastasis	Yes/no	16/17
Radiotherapy to venous tumor thrombus	Yes/no	14/19

†According to the Liver Cancer Group of Japan.
‡Venous invasion. Vv1, tumor thrombus in peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.
§Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

attending physician, one patient of Vv2 and five patients of Vv3 were enrolled. Since August 2006, the indication of 3D-CRT was limited to objective progressive VTT of Vv3 in principle, eight patients of Vv3 were enrolled. Patients received 3D-CRT in the Division of Radiation Oncology at our hospital. They received high-energy photon beam irradiation using 18, 10 or 6 MV, delivered by a three-dimensional conformal technique (CLINAC 2300 C/D or CLINACiX linear accelerators, Varian Medical Systems Inc., Palo Alto, CA, USA). The planning CT determined the gross tumor volume (GTV) representing only the VTT. The clinical target volume (CTV) was also determined; which included GTV and intrahepatic tumor forming the basal part of VTT. The planning target volume (PTV) represented the CTV plus a 10–20-mm margin in all directions for internal motion and set-up error. Four to five portal fields were used. The outlined target volumes, total liver tissue and organs at risk, including the spinal cord, bilateral kidneys, esophagus, stomach and other nearby intestinal tract targets, were transferred to the treatment planning system (Pinnacle 3, Philips Medical Systems, Eindhoven, The Netherlands) with reference to the diagnostic enhanced CT images. The prescribed dose was 30, 39 or 45 Gy, based on the dose-volume constraint of normal tissues and liver function. Using this protocol, it was estimated that 95% of the PTV should receive at least 95% of the prescribed dose, 50% of the liver tissue should not receive more than 25 Gy, 50% of each kidney not more than 20 Gy and that the maximum dose to the spinal cord, intestinal tract and esophagus was not more than 40 Gy. Finally, five patients received a total dose of 30 Gy, five patients 39 Gy and four patients 45 Gy, in daily doses of 3 Gy per fraction.

Evaluation

Every patient underwent dynamic CT before and after two courses of HAIC-5-FU/IFN, and the therapeutic effect was classified according to Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1[28] after completion of two cycles of the chemotherapy. A complete response (CR) was defined as disappearance of all target/non-target lesions, no appearance of any other lesion within 4 weeks, and normalization of α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP). CR was confirmed at 4 weeks after the first evalu-

ation of CR. A partial response (PR) was defined as a decrease of at least 30% in the sum of the longest diameter of target lesions with the baseline sum of the longest diameter of target lesions as the reference. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameter of target lesions. Stable disease (SD) was defined as meeting neither the PR nor PD criteria. We also evaluated the treatment effect of VTT by measuring the longest diameter to increase or decrease, the response of intrahepatic tumor to the therapy and overall systemic response. Adverse reactions were assessed every week during the treatment using the CTCAE. Radiotherapy-induced liver disease (RILD) exhibited the following criteria:[29] development of anicteric elevation of alkaline phosphatase level of at least twofold, nonmalignant ascites in the absence of documented progressive disease and increased transaminases levels of at least fivefold the upper limit of normal or of pretreatment level.

Statistical analysis

Data were analyzed statistically on 1 March 2011. Differences between background factors were examined for statistical significance using logistic regression test and Pearson's χ^2 test where appropriate. Consecutive data (e.g. α-fetoprotein) was classified by each median value referring to scatter diagram or histogram. Univariate analysis of predictors of survival was assessed by the cumulative survival rate, which was calculated from the initial date of HAIC-5-FU/IFN and assessed by the Kaplan–Meier life-table method, and differences were evaluated by the log rank test. Variables that achieved statistical significance ($P < 0.05$) or those with P-values of less than 0.10 on univariate analysis were entered into multivariate analysis. Multivariate analysis of predictors of survival was assessed by Cox proportional hazard model or Logistic regression analysis. All analyses were performed using the Statistical Package for Social Sciences (version 11, SPSS Inc., Chicago, IL). We assessed the survival benefits and safety of HAIC-5-FU/IFN combined with or without 3D-CRT to VTT.

RESULTS

Overall survival and response

FIGURE 1 SHOWS the cumulative survival rate of 33 patients who underwent HAIC using 5-FU/IFN. The median survival time (MST) was 7.9 months. The 1- and 2-year survival rates were 30% and 20%, respectively. The median observation time was 5.5 months (range, 0.7 to 54.9 months). Table 2 shows the response to therapy as evaluated by RECIST. In five patients (shown as NE), CT could not be performed after the HAIC. The systemic (i.e., whole body) response to the treatment was: CR in three cases, PR in five, SD in four and PD in 16, with an overall systemic response rate of 24%. We also defined intrahepatic (i.e., limited to the liver) response as one of the treatment factors in order to evaluate localized therapeutic effects in the liver. The intrahepatic response was: CR in three, PR in seven, SD in six and PD in 12, with an overall intrahepatic response rate of 30%, similar to the systemic response rate.

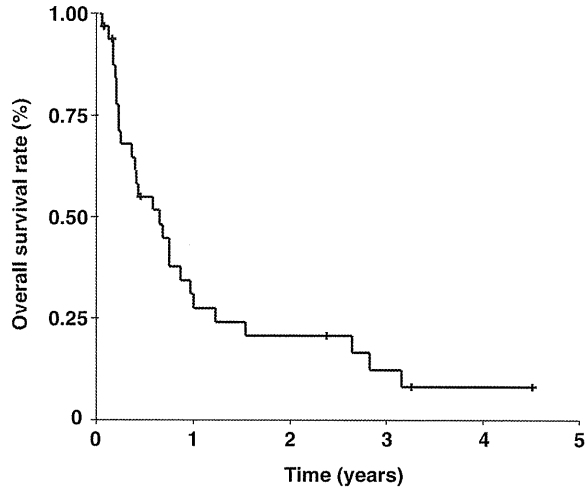

Figure 1 Overall survival of 33 patients with venous tumor thrombosis (VTT) treated by hepatic arterial infusion chemotherapy (HAIC). The median survival time (MST) was 7.9 months, and the 1- and 2-year survival rate were 30% and 20%, respectively. The median observation time was 5.5 months (range, 0.7–54.9 months).

Univariate analysis (Table 3) and multivariate analysis (Table 4) identified three factors that contributed to overall survival; treatment-related reduction in VTT

Table 2 Clinical response to the therapy to hepatocellular carcinoma (HCC) with venous tumor thrombus (VTT)

	CR	PR	SD	PD	NE	RR
Systemic evaluation of response: whole body	3	5	4	16	5	24%
Intrahepatic response: liver only	3	7	6	12	5	30%

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RR, response rate for patients with CR and PR per entire group of patients; SD, stable disease.

Table 3 Univariate analysis of factors that contributed to overall survival (Log rank test)

	Category	*n*	*P*-value
Sex	Female vs. male	3/30	0.567
Age (years)	≥65 vs. <65	18/15	0.326
ECOG PS	0 vs. 1	23/10	0.324
HCV Ab	Presence vs. absence	16/17	0.215
HBs Ag	Absence vs. presence	26/7	0.023
Child–Pugh stage	A vs. B	25/8	0.004
Previous treatment	No vs. yes	24/9	0.414
α-fetoprotein (ng/mL)	<5 000 vs. ≥5 000	17/16	0.559
des-γ-carboxy prothrombin (mAU/mL)	<10 000 vs. ≥10 000	14/19	0.309
Platelet count (/mm^3)	<150 000 vs. ≥150 000	19/14	0.0008
Size of largest tumor (mm)	<100 vs. ≥100	16/17	0.0003
Tumor liver occupying rate (%)	<50 vs. ≥50	20/13	0.0013
Grade of venous invasion (Vv)†	2 vs. 3	13/20	0.274
Grade of portal invasion (Vp)‡	0, 1, 2 vs. 3, 4	12/21	0.224
Extrahepatic metastasis	No vs. yes	17/16	0.040
Radiotherapy to venous tumor thrombus	Yes vs. no	14/19	0.667
Intrahepatic response	CR, PR vs. Other	10/23	0.0029
Effect of treatment on venous tumor thrombus	Decrease vs. increase	18/15	0.0001

†Venous invasion. Vv1, tumor thrombus in a second branch or more of peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.

‡Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

($P = 0.0006$, hazard ratio, HR, 6.611, 95% confidence interval [CI] 2.262–19.322), largest tumor size <100 mm ($P = 0.013$, HR 3.896, 95%CI 1.328–11.432), and intrahepatic response of complete response/partial response (CR/PR) ($P = 0.030$, HR 2.968, 95%CI 1.108–7.951). Patients classified as CR/PR based on intrahepatic response had a significantly longer MST than the non-CR/PR group (18.7 vs. 4.4 months, respectively, $P = 0.0029$, log rank test) (Fig. 2). Univariate analysis (Table 5) and multivariate analysis (Table 6) identified two factors that contributed to intrahepatic response of CR/PR; tumor liver occupying rate of >50% ($P = 0.016$, OR 23.239, 95%CI 1.791–301.508) and positivity for hepatitis C virus antibody (HCV Ab) ($P = 0.010$, OR 16.886, 95%CI 1.969–144.774).

Effect of radiotherapy

The clinical characteristics of patients treated by HAIC-5-FU/IFN with and without radiotherapy to VTT are summarized in Table 7. Patients treated with radiotherapy had a tendency to be elderly, hepatitis B virus

Table 4 Multivariate analysis for factors that contribute to overall survival, Cox proportional hazards model with stepwise selection

	Category	HR	95% CI	*P*-value
Effect of treatment of venous tumor thrombus	Decrease	6.611	2.262–19.322	0.0006
	Increase	1		
Size of largest tumor (mm)	<100	3.896	1.328–11.432	0.013
	≥100	1		
Intrahepatic response	CR, PR	2.968	1.108–7.951	0.030
	Other	1		

95% CI, 95% confidence interval; CR, complete response; HR, Hazard ratio, PR, partial response.

(HBV) negative and HCV positive. About two-thirds of patients with VTT of Vv3 received 3D-CRT. Figure 3 shows the overall response to treatment of all patients classified according to the application of 3D-CRT. In patients who received HAIC alone, five out of 19 patients were classified as CR/PR based on intrahepatic response, with a response rate of 26%. Furthermore, VTT was considered to have decreased in seven out of 19 patients with a VTT-treatment effective rate of 37%. For patients who received HAIC combined with radiotherapy, CR/PR was achieved in five out of 14 patients, with a response rate of 36%, and VTT decreased in 11 out of 14 patients, with a treatment effective rate of up to 79%. Radiotherapy had no significant effect on the intrahepatic response ($P = 0.561$, Pearson's χ^2 test). The combination of HAIC and radiotherapy had a significant effect on VTT ($P = 0.017$, Pearson's χ^2 test). Table 8 shows the results of univariate analysis for factors that contributed to the effect of treatment on VTT. Multivariate analysis (Table 9) two factors that significantly and independently influenced the VTT; platelet count less than 150 000/mm^3 ($P = 0.015$, OR 16.087, 95%CI 1.704–151.861) and response of VTT to radiotherapy ($P = 0.021$, OR 14.982, 95%CI 1.508–148.827). Figure 4 shows the cumulative survival rates of 16 patients with VTT in the inferior vena cava (Vv3), based on the VTT response to 3D-CRT. The nine patients who received HAIC-5-FU/IFN and 3D-CRT to VTT and showed a decrease in VTT had a significantly longer MST of 9.2 months ($P = 0.028$, log rank test), compared with the seven patients who received HAIC-5-FU/IFN without or with ineffective 3D-CRT (these patients showed increases in VTT and MST of 3.1 months).

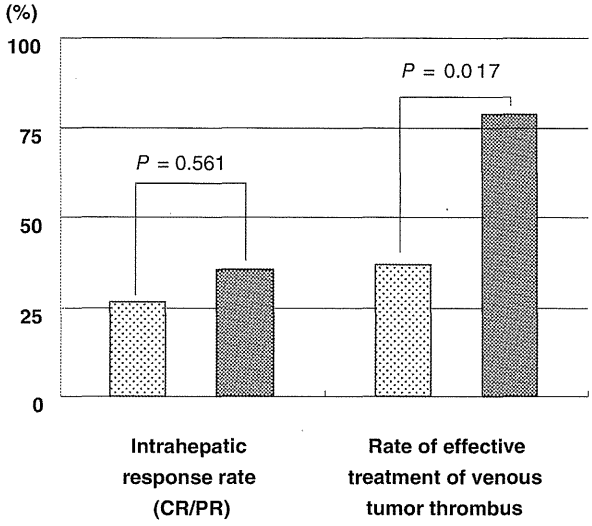

Figure 3 Overall treatment response according to the treatment regimen presence or absence of undergoing radiotherapy to venous tumor thrombus (VTT). ▨, HAIC alone; ▩, HAIC plus 3-D conformal radiotherapy (3D-CRT). HAIC, hepatic arterial infusion chemotherapy.

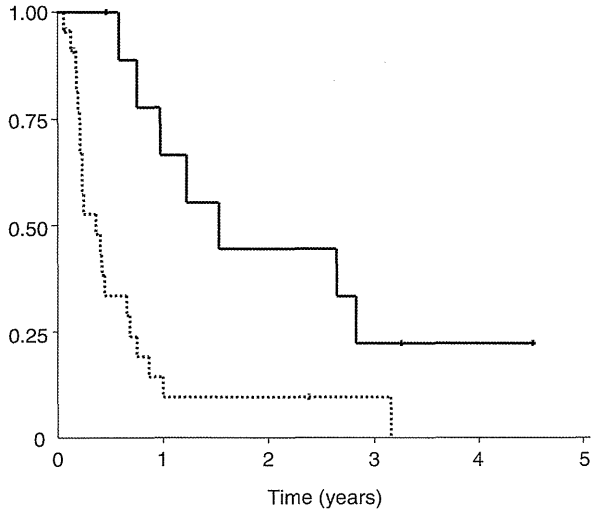

Figure 2 Cumulative survival rate of 33 patients with venous tumor thrombosis (VTT) treated by hepatic arterial infusion chemotherapy (HAIC). Solid line: 10 patients, who underwent HAIC and classified as complete response/partial response (CR/PR) based on intrahepatic response, had a significantly longer median survival time (MST) of 18.7 months ($P = 0.0029$, log rank test). Dashed line: 23 patients who were classified as non-CR/PR based on intrahepatic response resulting in MST of 4.4 months. ——, CR/PR of intrahepatic response; ·····, Non-CR/PR of intrahepatic response.

Incidence of extrahepatic metastasis

Figure 5 shows the cumulative rate of extrahepatic metastases in 17 patients who were negative for extrahepatic metastasis before HAIC-5-FU/IFN. Eight (47%) patients developed extrahepatic metastases after starting HAIC-5-FU/IFN, including seven with lung metastases and one with adrenal gland metastasis. The median time to the diagnosis of metastasis was 7.1 months. The 6- and 12-month cumulative incidence rates were 30% and 56%, respectively. The median survival time was 4.4 months after the diagnosis of extrahepatic metastasis.

Other anti-cancer treatments

Nine out of 33 (27%) patients received additional courses of HAIC with 5-FU/IFN after completing the two

Table 5 Univariate analysis for factors that contribute to intrahepatic response after two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment, Pearson's χ^2 test

	Category	*n*	*P*-value
Sex	Female vs. male	3/30	0.905
Age (years)	≥65 vs. <65	18/15	0.103
ECOG PS	0 vs. 1	23/10	0.980
HCV Ab	Presence vs. absence	16/17	0.017
HBs Ag	Absence vs. presence	26/7	0.299
Child–Pugh stage	A vs. B	25/8	0.208
Previous treatment	No vs. yes	24/9	0.061
α-fetoprotein (ng/mL)	<5 000 vs. ≥5 000	17/16	0.520
des-γ-carboxy prothrombin (mAU/mL)	<10 000 vs. ≥10 000	14/19	0.561
Platelet count (/mm^3)	<150 000 vs. ≥150 000	19/14	0.086
Size of largest tumor (mm)	<100 vs. ≥100	16/17	0.103
Tumor liver occupying rate (%)	<50 vs. ≥50	20/13	0.023
Grade of venous invasion (Vv)†	2 vs. 3	13/20	0.020
Grade of portal invasion (Vp)‡	0, 1, 2 vs. 3, 4	12/21	0.963
Extrahepatic metastasis	No vs. yes	17/16	0.497
Radiotherapy to venous tumor thrombus	Yes vs. no	14/19	0.161

†Venous invasion. Vv1, tumor thrombus in a second branch or more of peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.

‡Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

recommended courses. On the other hand, 24 out of 33 (73%) patients did not complete HAIC-5-FU/IFN. Subsequently, 21 (64%) patients received other anti-cancer treatments, and 12 patients (36%) received best supportive care (BSC). The other treatments included TACE in 17 patients (MST 8.3 months), HAIC in six patients (MST 14.9 months) and systemic chemotherapy in six patients (MST 2.8 months). The MST of the additional treatment group was 11.8 months, which was significantly longer than the BSC group (with MST of 3.0 months, $P = 0.0078$, Log rank test). With regard to the regimens of other treatments, trans-arterial treatments tended to be associated with longer survival than systemic chemotherapy and BSC.

Adverse reactions and complications

Fever, fatigue, nausea and anorexia were the most common adverse events, but these were mostly CTCAE grade 1 or 2. CTCAE grade 3 or 4 adverse reactions included leukopenia in five patients (15%), thrombocytopenia in two (6%), anemia in three (9%) and anorexia in two (6%). Six patients required treatment with granulocyte colony-stimulating factor for leukopenia. Three patients required blood transfusion, but none

Table 6 Multivariate analysis for factors that influenced intrahepatic response to two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment. Logistic regression analysis

Factors	Category	OR	95% CI	*P*-value
Tumor liver occupying rate (%)	<50	23.239	1.791–301.508	0.016
	≥50	1		
HCV Ab	Presence	16.886	1.969–144.774	0.010
	Absence	1		

95% CI, 95% confidence interval; HCV Ab, hepatitis C virus antibody; OR, odds ratio.

Table 7 Clinical characteristics of patients with venous tumor thrombus treated by hepatic arterial infusion chemotherapy (HAIC) using 5-fluorouracil (5-FU) and systemic interferon (IFN)-α (HAIC-5-FU/IFN) with and without radiotherapy to venous tumor thrombus, Pearson's χ^2 test

Clinical characteristics	Category	Total ($n = 33$)	HAIC alone ($n = 19$)	HAIC plus radio therapy ($n = 14$)	*P*-value
Sex	Male/female	30/3	18/1	12/2	0.373
Age (years)	<65/≥65	15/18	11/8	4/10	0.024
ECOG PS	0/1	23/10	14/5	9/5	0.561
HCV Ab	+/−	16/17	6/13	10/4	0.024
HBs Ag	+/−	7/26	7/12	0/14	0.011
Child–Pugh stage	A/B	25/8	16/3	9/5	0.187
Previous treatment	Yes/no	9/24	3/16	6/8	0.084
α-fetoprotein (ng/mL)	<5 000/≥5 000	17/16	8/11	9/5	0.208
des-γ-carboxy prothrombin (mAU/mL)	<10 000/≥10 000	14/19	9/10	5/9	0.503
Platelet count (/mm^3)	<150 000/≥150 000	19/14	11/8	8/6	0.966
size of largest tumor (mm)	<100/≥100	16/17	11/8	5/9	0.208
Tumor liver occupying rate (%)	<50/≥50	20/13	11/8	9/5	0.710
Grade of venous invasion (Vv)†	Vv 2/3	13/20	12/7	1/13	0.001
Grade of portal invasion (Vp)‡	Vp 0,1,2/3,4	12/21	6/13	6/8	0.506
Extrahepatic metastasis	Yes/no	16/17	9/10	7/7	0.881

†Venous invasion. Vv1, tumor thrombus in a second branch or more of peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.

‡Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

required platelet transfusion. Cutaneous ulcerations developed in the inguinal region in four patients, requiring implantation of reservoir system. Furthermore, two patients developed bleeding esophageal varices at one month after completion of HAIC-5-FU/IFN. Three patients developed radiation esophagitis, which required hospitalization as CTCAE grade 3. Of the latter group, one developed esophageal stenosis requiring endoscopic dilatation at 2 months after completion of radiotherapy. None of the patients who received the combination of HAIC-5-FU/IFN and radiotherapy developed hepatic failure that fulfilled the criteria of RILD.[29] On the other hand, three patients who did not receive 3D-CRT developed hepatic failure with hyperbilirubinemia; the cause of hepatic failure was considered to be the rapid progression of intrahepatic HCC.

Causes of death

At the time of analysis, six patients were still alive, whereas 27 patients had died. All 27 deaths were cancer-related, with the majority being due to progression of intrahepatic HCC. Among them, three patients died of HCC rupture and intra-abdominal bleeding. Two patients who did not receive 3D-CRT died of esophageal variceal bleeding. None died directly of extrahepatic metastases, and one patient died of septic necrotizing limb fasciitis. During the periods of treatment, we have no sudden death patient, which was clinically suspected to be due to pulmonary artery embolism.

DISCUSSION

INVASION OF A major vessel, especially the trunk of PVTT, is a poor prognostic factor in patients with advanced HCC.[14–19] Furthermore, the best available treatment for advanced HCC with PVTT is considered HAIC-5-FU/IFN.[9–13] Based on the lack of sufficient information on the efficacy of HAIC-5-FU/IFN for advanced HCC with VTT in the hepatic vein trunk (Vv2) or inferior vena cava (Vv3), we investigated the efficacy of HAIC-5-FU/IFN for HCC with VTT in this retrospective study. We also investigated the response to the combination of HAIC-5-FU/IFN and 3D-CRT to VTT of Vv3. In 33 patients, the intrahepatic response rate to HAIC-5-FU/IFN was 30%,

Table 8 Univariate analysis for determinants of effect of treatment on venous tumor thrombus after two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment, Pearson's χ^2 test

Factors	Category	*n*	*P*-value
Sex	Female vs. male	3/30	0.658
Age (years)	≥65 vs. <65	18/15	0.112
ECOG PS	0 vs. 1	23/10	0.730
HCV Ab	Presence vs. absence	16/17	0.112
HBs Ag	Absence vs. presence	26/7	0.120
Child–Pugh stage	A vs. B	25/8	0.767
Previous treatment	No vs. yes	24/9	0.943
α-fetoprotein (ng/mL)	<5 000 vs. ≥5 000	17/16	0.611
des-γ-carboxy prothrombin (mAU/mL)	<10 000 vs. ≥10 000	14/19	0.335
Platelet count (/mm^3)	<150 000 vs. ≥150 000	19/14	0.010
Size of largest tumor (mm)	<100 vs. ≥100	16/17	0.112
Tumor liver occupying rate (%)	<50 vs. ≥50	20/13	0.027
Grade of venous invasion (Vv)†	2 vs. 3	13/20	0.135
Grade of portal invasion (Vp)‡	0, 1, 2 vs. 3, 4	12/21	0.290
Extrahepatic metastasis	No vs. yes	17/16	0.227
Radiotherapy to venous tumor thrombus	Yes vs. no	14/19	0.017

†Venous invasion. Vv1, tumor thrombus in a second branch or more of peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.

‡Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

with MST of 7.9 months. Multivariate analysis (Table 6) identified two factors that influenced the intrahepatic response to HAIC-5-FU/IFN: tumor liver occupying rate of >50% ($P = 0.016$) and positivity for HCV Ab ($P = 0.010$). The combination of HAIC-5-FU/IFN with 3D-CRT to VTT had a significantly better treatment effective rate of VTT (79%) than HAIC-5-FU/IFN alone (37%). Multivariate analysis (Table 4) identified three independent factors that influenced survival: treatment-related reduction in VTT ($P = 0.0006$), largest tumor size <100 mm ($P = 0.013$), and CR/PR for intrahepatic response ($P = 0.030$). While 3D-CRT did not significantly improve the survival times, it significantly reduced VTT, thus indirectly contributing to the high intrahepatic response and presumably improving the survival rate. Among 16 patients with disadvantageous conditions (VTT-Vv3 and non-CR/PR), effective 3D-CRT resulted in significant prolongation of survival time compared with patients who did not receive or showed ineffective response to 3D-CRT ($P = 0.028$, Fig. 4). This result suggests the prognostic value of radiotherapy to VTT for advanced HCC patients treated by HAIC-5-FU/IFN.

The response rate to HAIC-5-FU/IFN in HCC with VTT (30%) was similar to the previously reported response

Table 9 Multivariate analysis for factors that contributed to the effect of treatment on venous tumor thrombus after two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment. Logistic regression analysis

	Category	OR	95% CI	*P*-value
Platelet count (/mm^3)	<150 000	16.087	1.704–151.861	0.015
	≥150 000	1		
Radiotherapy to venous tumor thrombus	Yes	14.982	1.508–148.827	0.021
	No	1		

95% CI, 95% confidence interval; OR, odds ratio.

rate to HAIC-5-FU/IFN in HCC with PVTT (29–52%).[9,12,13] Multivariate analysis found that tumor liver occupying rate ($P = 0.016$) and positivity for HCV Ab ($P = 0.010$) contributed to intrahepatic response of CR/PR (Table 6). Two previous studies[9,13] also reported that positivity for HCV Ab was also a pretreatment predictive factor for response and survival of advanced HCC treated with HAIC-5-FU/IFN. The exact reason for the correlation between HCV positivity and the response to HAIC-5-FU/IFN is not clear. Several studies have investigated the differences between the HCV and HBV in relation to HCC, such as the mechanism of hepatocarcinogenesis[30,31] and cytokine pattern in hepatitis.[32] These factors could influence the tumor response to therapy.

Similar to a previous report on advanced HCC with PVTT treated by HAIC-5-FU/IFN,[9,12,13] patients classified as CR/PR based on intrahepatic response had a significantly longer MST than the non-CR/PR group (18.7 vs. 4.4 months, respectively, $P = 0.0029$, log rank test) (Fig. 2). Multivariate analysis showed that survival correlated with effect of treatment VTT ($P = 0.0006$), tumor size ($P = 0.013$) and CR/PR based on intrahepatic response ($P = 0.030$) (Table 4).

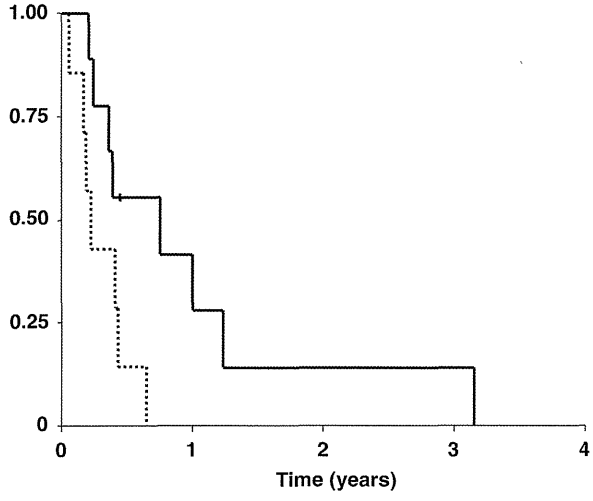

Figure 4 Cumulative survival rate of 16 patients with advanced hepatocellular carcinoma (HCC) and venous tumor thrombosis (VTT) of Vv3 who were not evaluated as complete or partial response (non-CR/PR). Solid line: nine patients who underwent arterial infusion chemotherapy (HAIC) and responded to 3-D conformal radiotherapy (3D-CRT), resulting in a decrease in VTT and significantly longer median survival time (MST) of 9.2 months ($P = 0.028$, log rank test). Dashed line: seven patients who underwent HAIC without or with ineffective radiotherapy, resulting in increase of VTT and MST of 3.1 months. ——, Effective 3D-CRT to VTT; ·····, No or ineffective 3D-CRT to VTT.

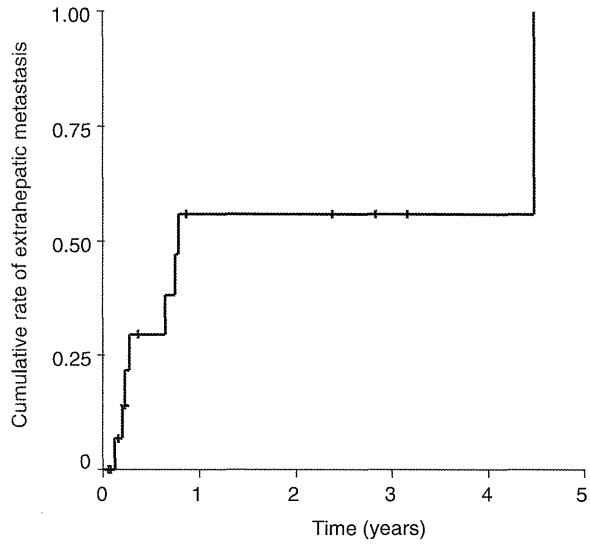

Figure 5 Cumulative rate of extrahepatic metastasis in 17 patients who were negative for extrahepatic metastasis at baseline (before treatment). The median time to metastasis was 7.1 months. The 6- and 12-month cumulative rate of metastasis was 30% and 56%, respectively. HAIC, hepatic arterial infusion chemotherapy; non-CR/PR, not evaluated complete or partial response on intrahepatic response evaluation; VTT, venous tumor thrombus; Vv3, tumor thrombus in the inferior vena cava.

The highest response rate was registered with the combination of HAIC-5-FU/IFN and 3D-CRT to VTT (79%, Fig. 3). This finding is similar to that reported by Katamura *et al.*[27] who reported a rate of 75% for HAIC-5-FU/IFN with radiotherapy to PVTT. Although 3D-CRT was considered, in general, tolerable to allow continuation of HAIC-5-FU/IFN without the development of RILD in our study, radiotherapy caused severe esophageal complications in three out of 14 patients (21%). This finding suggests that it is often difficult to avoid the harmful effect of irradiation to the radiosensitive esophagus, which is anatomically close to VTT of Vv3. Careful planning of 3D-CRT and reduction of radiation dose as much as possible might avoid esophageal complications associated with 3D-CRT of Vv3.

Although the response of VTT to radiotherapy was high in this study, the addition of 3D-CRT to the management of advanced HCC with VTT did not improve survival ($P = 0.667$, log rank test). This result could be causally related to the existence of five patients in HAIC-

5-FU/IFN alone group who achieved CR/PR without 3D-CRT and obtained prolonged survival (MST 34.3 months). These long-term survivors in the HAIC-5-FU/IFN alone group might balance out the benefit of additional 3D-CRT in the HAIC-5-FU/IFN plus radiotherapy group. With regard to the prognostic effect of 3D-CRT, radiotherapy and the associated reduction of VTT significantly improved the survival time in patients of non-CR/PR (intrahepatic response) group with VTT of Vv3 ($P = 0.028$, Fig. 4). In other words, patients who fail to show a response to HAIC-5-FU/IFN, 3D-CRT should be applied with the hope of improving survival. Conversely, the response to radiotherapy would be rather questionable in patients who show CR/PR response to HAIC-5-FU/IFN alone. Because the response of HCC with VTT to HAIC-5-FU/IFN cannot be predicted before treatment, it is important to monitor the patients on HAIC-5-FU/IFN for the response to such treatment as soon as possible, and introduce 3D-CRT to VTT to those who show non-CR/PR.

Despite the relatively high efficacy of the HAIC-5-FU/IFN regimen, the high incidence of extrahepatic metastasis is a poor prognostic sign. In the seven patients who were confirmed to be metastasis-free at baseline and developed extrahepatic metastasis during HAIC-5-FU/IFN treatment, the MST was 4.4 months after the detection of metastasis. In other words, the prognosis of these patients was similar to those who presented with extrahepatic metastasis before HAIC-5-FU/IFN (MST, 3.0 months). Various chemotherapies have been used for HCC extrahepatic metastasis though a standard regimen has not yet been established. Nevertheless, some investigators reported an objective response rate of 17–25% using systemic combination chemotherapy of S1 and IFN.[33,34]

Recent studies have praised the benefits of sorafenib tosilate in unresectable advanced HCC, reporting relatively long MST of 6.5–10.7 months and slowing of radiological progression in nearly 3 months.[35,36] While sorafenib seems to have survival benefits, the reported response rate is less than 2%. Compared with our results, with MST of 7.9 months, systemic RR of 24% and intrahepatic RR of 30% for advanced HCC with VTT, HAIC-5-FU/IFN seems to be characterized by higher response rate than sorafenib monotherapy, while MST was similar. Because the intrahepatic CR/PR patients by HAIC-5-FU/IFN could obtain significantly longer survival than the non-CR/PR patients (18.7 vs. 4.4 months, respectively), it might be meaningful to sort out HAIC-5-FU/IFN effective HCC patients who have potentially prolonged prognosis by HAIC-5-FU/IFN before introducing sorafenib treatment. There seemed to be a limitation of HAIC-5-FU/IFN that extrahepatic metastasis frequently occurred as a poor prognostic sign. In others, the benefits of sorafenib were reported to be consistent including patients with extrahepatic spread.[35,36] Sorafenib might be one of the most prospective modalities for extrahepatic metastasis after ineffective HAIC-5-FU/IFN.

The present study has certain limitations. These include data generated from a single institution, small population size and retrospective study design. For example, patients had a tendency to be elderly, HBV negative and HCV positive in comparison between the HAIC-5-FU/IFN alone group and the HAIC-5-FU/IFN plus 3D-CRT group (Table 7). There seemed to be no doubt about some clinicopathologic biases in patient background due to our study design. However, our results provide material for future large scale studies to determine the usefulness of the combination of HAIC-5-FU/IFN and 3D-CRT for advanced HCC with VTT.

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