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ORIGINAL ARTICLE

A phase II trial of transcatheter arterial infusion chemotherapy with an epirubicin-Lipiodol emulsion for advanced hepatocellular carcinoma refractory to transcatheter arterial embolization

Tsutomu Tanaka · Masafumi Ikeda · Takuji Okusaka · Hideki Ueno · Chigusa Morizane · Takashi Ogura · Atsushi Hagihara · Satoru Iwasa

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Abstract
Introduction Transcatheter arterial embolization (TAE) has been recognized as an effective palliative treatment option for advanced hepatocellular carcinoma (HCC). However, no effective alternative treatments for TAE-refractory HCC have yet been established. The aim of this study was to evaluate the antitumor activity and toxicity of transcatheter arterial infusion chemotherapy using an epirubicin-Lipiodol emulsion in patients with TAE-refractory HCC.
Methods Patients with TAE-refractory HCC were enrolled. A dose of 60 mg/m^2 epirubicin emulsified in Lipiodol and contrast medium was administered from the feeding artery of the HCC. Treatment was repeated every 4 to 12 weeks if there was no evidence of tumor progression or unacceptable toxicity.
Results Twenty patients were enrolled in this trial. The median number of treatment courses was 1 (range 1–4). Among the enrolled patients, one (5%) achieved a partial response, and three (15%) showed a minor response. Five (25%) patients had no change and 11 (55%) showed progressive disease. The median survival time, 1-year survival rate and median progression-free survival time for the patients as a whole were 12.4 months, 52.6%, and 1.1 months, respectively. The main grade 3 and 4 toxicities were leukocytopenia (35%), neutropenia (65%), thrombocytopenia (30%), and elevations of the aspartate aminotransferase (45%) and alanine aminotransferase (35%) levels. These toxicities were generally brief and reversible.
Conclusion Transcatheter arterial infusion chemotherapy with an epirubicin-Lipiodol emulsion appears to have only modest activity with moderate toxicity for treatment of patients with TAE-refractory HCC. These findings do not support its use in practice, and further studies with the same regimen in patients with TAE-refractory HCC are not recommended.

Keywords Hepatocellular carcinoma · Transcatheter arterial infusion chemotherapy · Epirubicin · Transcatheter arterial embolization

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer death in Japan. Screening of populations at high risk for HCC has increased the number of candidates for curative treatments such as hepatic resection and local ablative therapy [1, 19]. However, the prognosis of patients with HCC is still unsatisfactory, mainly because of post-therapeutic recurrence. Several therapies have been applied for patients with recurrence and those with advanced disease at initial diagnosis. Radioembolization using yttrium-90 microspheres has been used frequently for advanced HCC because of its favorable efficacy [3]. However, its usefulness has not been fully elucidated in randomized controlled trials in comparison with other treatments. Transcatheter arterial embolization (TAE) has been widely carried out [11, 17]. Recently, two randomized control trials and a meta-analysis have reported the survival benefits of TAE, which now plays a major role in the nonsurgical

T. Tanaka · M. Ikeda (✉) · T. Okusaka · H. Ueno · C. Morizane · T. Ogura · A. Hagihara · S. Iwasa
Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: masikeda@ncc.go.jp

treatment of HCC [8–10] However, no effective alternative treatments for TAE-refractory HCC have yet been established.

Transcatheter arterial infusion chemotherapy (TAI) is often used for the treatment of advanced HCC, but a consensus regarding the most effective chemotherapeutic regimen has not been reached [12, 16, 20]. Anthracycline anticancer agents are considered to be among the most effective agents for HCC [7]. Epirubicin, an anthracycline agent, is the most commonly used anticancer agent for advanced HCC in Japan. It exerts its anticancer effect by inhibiting DNA polymerase and RNA polymerase reactions, and suppresses the biosynthesis of both DNA and RNA by forming a complex with tumor cell DNA. Among patients with unresectable HCC, the rate of response to TAI with epirubicin has been reported to be 15% [13]. Lipiodol, a lipid lymphographic agent, is selectively retained by HCC cells for prolonged periods in comparison with normal cells, and is therefore commonly mixed with anticancer agents to retain them in the target tumor [14, 15, 23]. In randomized trials of TAI therapy comparing epirubicin with and without Lipiodol, an emulsion of epirubicin and Lipiodol (response rate 42%) was found to be more effective than epirubicin alone (response rate 12%) [22]. It is suggested that TAI with an emulsion of anticancer agent and Lipiodol can exert more potent effects than use of an anticancer agent alone. On the basis of these observations, we have conducted a phase II trial of TAI using an epirubicin-Lipiodol emulsion in patients with TAE-refractory HCC to evaluate its antitumor effect and toxicity.

Patients and methods

Patients

Each patient was required to meet the following criteria: (1) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (2) an age of over 20 years, (3) a diagnosis of HCC based on histological findings or typical angiography and computed tomography (CT) findings, (4) no indications for surgical resection or local ablative therapy, such as percutaneous ethanol injection and radiofrequency ablation, (5) TAE-refractory tumor(s), (6) a hepatic artery with a structure appropriate for hepatic arterial catheterization therapy, (7) hypervascular tumor(s) showing enhancement during angiography, (8) bidimensionally measurable hepatic lesions, (9) adequate hematological function (white blood cell count $\geq$3,000/mm^3, platelets $\geq$75,000/mm^3, hemoglobin $\geq$10 g/dl), adequate hepatic function (serum total bilirubin $\leq$3.0 mg/dl, serum albumin $\geq$3.0 g/dl, serum aspartate transferase (AST)/serum alanine aminotransferase (ALT) $\leq$5 times the upper normal limit, adequate renal function (serum creatinine $\leq$ the upper normal limit), (10) an estimated life expectancy of more than 8 weeks after study entry, (11) no HCC treatment for 4 weeks before study entry, and (12) written informed consent. TAE-refractory tumors were defined as those showing an increase or a reduction of less than 25% in the size of hypervascular lesions as visualized by dynamic CT at 4 weeks after TAE, and elevation of tumor markers including alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II was not included in this definition.

Patients were excluded if they met the following criteria: (1) a history of allergy to iodine-containing agents and/or contrast media, (2) concomitant malignancy, (3) extrahepatic metastasis, (4) tumor thrombus in the main trunk and/or first branch of the portal vein, (5) refractory ascites or pleural effusion, (6) active gastrointestinal bleeding, (7) serious heart disease, (8) pregnant or lactating women, or women of childbearing potential, and (9) other serious medical conditions. The phase II trial was approved by the institutional review board of the National Cancer Center.

Treatment

The catheter was inserted through the femoral artery using the Seldinger method. Angiography of the celiac trunk and superior mesenteric artery was performed to visualize the arterial vascularization of the liver and to evaluate portal vein patency. After detection of tumor staining and the supplying artery, a dose of 60 mg/m^2 epirubicin emulsified in 6 ml of Lipiodol and 6 ml of non-ionic contrast medium was delivered directly into the feeding artery under fluoroscopic guidance. If there was no evidence of tumor progression or unacceptable toxicity, the treatment was repeated. The relatively long treatment duration was designed as 4–12 weeks in consideration of the low treatment tolerance of the enrolled patients, because they had suffered liver damage due to the previous TAE. Tumor progression was defined as more than 25% enlargement of all measurable lesions, or appearance of new lesions, as visualized by dynamic CT. Patients whose tumors were refractory to this regimen were allowed to receive other treatment.

Response and toxicity evaluation

Before this treatment, a complete medical history was taken, together with a physical examination, and laboratory data including a complete blood count, and chemistry and coagulation parameters, were obtained. A complete blood count and chemical parameters were obtained at least once a week for 2 weeks after treatment. Tumor makers were measured every 4 weeks.

The antitumor effect was evaluated by dynamic CT, which was performed 4 weeks after the treatment. The area of Lipiodol accumulation and the area of hypoattenuation without contrast enhancement in the early phase of dynamic CT were evaluated as the area of tumor necrosis. The response was assessed as follows: complete response (CR), complete disappearance or 100% necrosis of all tumors with no evidence of new lesions; partial response (PR), more than 50% reduction and/or more than 50% necrosis of all measurable lesions with no evidence of new lesions; minor response (MR), 25–50% reduction and/or 25–50% necrosis of all measurable lesions with no evidence of new lesions; progressive disease (PD), more than 25% enlargement of all measurable lesions or appearance of new lesions; no change (NC), disease not qualifying for classification as CR, PR, MR, or PD. Toxicity was assessed according to the criteria of the Japan Society for Cancer Therapy, which is fundamentally similar to the World Health Organization criteria [5].

Statistical consideration

The primary endpoints were the treatment response rate and toxicity, and the secondary endpoints were survival and progression-free survival. The number of patients enrolled was planned using a two-step design based on assumptions that the expected response rate was 20%, the threshold response rate was defined as 5%, the alpha error was 10%, and the beta error was 20%. An interim analysis was planned when 10 patients were enrolled in the first stage of the study. If no patient had a PR or CR, this treatment was judged to be ineffective and the study was to be ended. If a response was detected in any of the first ten patients studied, an additional 10 patients were to be studied in a second stage of accrual to estimate the response rate. Overall survival and progression-free survival were calculated by the Kaplan–Meier method [6].

Results

Patient characteristics

A total of 20 patients were enrolled between April 1998 and August 2004 at the National Cancer Center Hospital, and all of these patients received the treatment. The characteristics of the patients are listed in Table 1. All patients were men with the median age of 66 years (range, 37–81 years) and had a good ECOG performances status of 0–1. There were 18 (90%) and 2 (10%) patients with Child-Pugh Stage A and B, respectively. The median number of previous TAE sessions was 3 (range 1–8), and the median period from the first TAE to the date on which the tumors were judged to be TAE-refractory was 16.5 months (range 1.1–104.7 months). The median diameter of the largest tumor was 28 mm (range 15–69). A tumor thrombus in a third branch of the portal vein was observed in two patients.

Table 1 Patient characteristics

Characteristics	No of patients (%)
Age	
Median [range]	66 [37–81]
Sex	
Men	20 (100)
Performance status[a]	
0	15 (75)
1	5 (25)
Hepatitis B surface antigen	
Positive	4 (25)
Hepatitis C virus antibody	
Positive	17 (85)
History of resection	12 (60)
History of local ablative therapy	10 (50)
No of previous TAE[b]	
Median [range]	3 [1–8]
Child-Pugh stage	
A	18 (90)
B	2 (10)
Alpha-fetoprotein (ng/dL)	
Median [range]	294 [24–33,790]
PIVKA II[c] (mAU/mL)	
Median [range]	571 [12–10,410]
Tumor stage[d]	
II	17 (85)
IIIA	3 (15)
No of tumors	
2–4	6 (30)
≥5	14 (70)
Portal vein tumor thrombus	
Present	2 (10)

[a] Criteria of the Eastern Cooperative Oncology Group

[b] Transcatheter arterial embolization

[c] Protein induced by the absence of vitamin K or antagonist II

[d] The TMN classification according to the International Union Against Cancer. (5th Edition)

Treatments

The median number of treatment courses in this study was 1 (range 1–4). Treatment was discontinued in all 20 patients due to disease progression. Eight patients underwent the following therapies after this study: TAE with mitomycin C in five patients, TAI with mitomycin C in one patient, TAI with doxorubicin in one patient and TAI with

cisplatin in one patient. The remaining 12 patients did not receive any other anticancer treatment for their HCC.

Efficacy

All patients were assessable for analysis of efficacy and toxicity. One patient achieved PR (5%), with an overall response rate of 5% (95% confidence interval 0–25%), and three (15%) showed MR. Five (25%) and 11 (55%) patients showed NC and PD, respectively. Survival curves are shown in Fig. 1. The median survival time, the 1-year survival rate and median progression-free survival time for all patients were 12.4 months, 52.6% and 1.1 months, respectively. The results for time to progression and progression-free survival were the same in this study. During the treatments, the serum alpha-fetoprotein level was reduced by ≥50% in 3 of 11 (27%) patients who had shown a pretreatment level of ≥100 ng/dl, and the serum level of protein induced by vitamin K absence or antagonist-II was reduced by ≥50% in 5 of 14 (36%) patients who had shown a pretreatment level of ≥100 mAU/ml (Fig. 2).

Toxicity

The hematological and non-hematological toxicities are summarized in Table 2. Among hematological toxicities, grade 3–4 leukocytopenia, neutropenia and thrombocytopenia were observed in 7 (35%), 13 (65%) and 6 (30%) patients, respectively. Febrile neutropenia was observed in three (15%) patients. These toxicities returned to the initial level within four weeks after the treatments. Among the non-hematological toxicities, grade 3 elevated AST and ALT levels were observed in 12 patients (60%) and 7 (35%), respectively. There were no other grade 3–4 non-hematological toxicities. Cardiotoxicity was not observed in any of the patients.

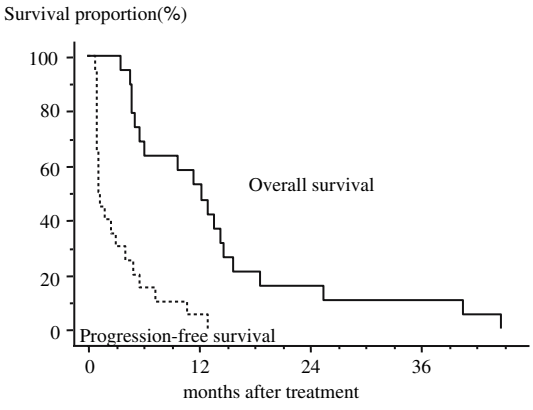

Fig. 1 Overall and progression-free survival curves of 20 patients treated with transcatheter arterial infusion chemotherapy using epirubicin-lipiodol emulsion for advanced hepatocellular carcinoma refractory to transcatheter arterial embolization

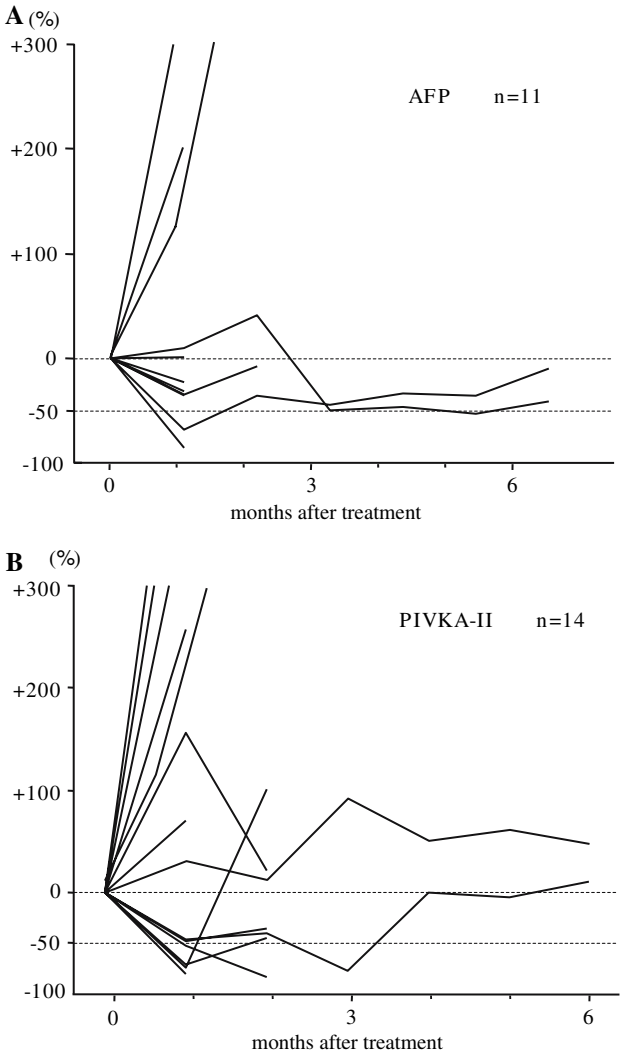

Fig. 2 **a** Serial changes in serum level of alpha-fetoprotein in each patient who had shown a pretreatment level of ≥100 ng/dL. **b** Serial changes in serum level of protein induced by vitamin K absence or antagonist-II in each patient who had shown a pretreatment level of ≥100 mAU/mL

Discussion

There is no standard anticancer therapy for patients with TAE-refractory HCC. As an anticancer therapy for such patients, TAI therapy was planned in this study for the following reasons. First, TAI can deliver higher concentrations of anticancer agents to HCC than systemic chemotherapy, because the anticancer agents flow directly into the HCC through the hepatic artery. Secondly, their systemic distribution and accompanying adverse effects can be minimized, because the agents are largely metabolized in the liver [2, 18]. As an anticancer agent, epirubicin is recognized to be effective, and is widely used for treatment

Table 2 Toxicity

	No of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Hematological toxicity					
Anemia	6	5	0	0	0 (0)
Leukocytopenia	7	5	7	0	7 (35)
Neutropenia	1	2	8	5	13 (65)
Thrombocytopenia	5	6	6	0	6 (30)
Non-hematological toxicity					
Nausea/emesis	7	1	0	0	0 (0)
Fever	10	4	0	0	0 (0)
Diarrhea	0	0	0	0	0 (0)
Fatigue	2	0	0	0	0 (0)
Alopecia	7	0	0	0	0 (0)
Elevated total bilirubin level	12	7	0	0	0 (0)
Elevated aspartate aminotransferase level	3	8	9	0	9 (45)
Elevated alanine aminotransferase level	8	5	7	0	7 (35)
Elevated alkaline phosphatase level	12	4	0	0	0 (0)
Elevated creatinine level	0	1	0	0	0 (0)

of advanced HCC [5, 7]. In addition, anticancer agent-Lipiodol emulsion is reported to exert a more potent antitumor effect than anticancer agent alone [22]. Therefore, the effect of TAI with epirubicin-Lipiodol emulsion for TAE-refractory HCC was evaluated in this study.

Yoshikawa et al. [22] reported that the rate of response to TAI with epirubicin-Lipiodol emulsion (a mixture of 70 mg/body epirubicin and 2–3 ml Lipiodol) for advanced HCC was 42%. Sumie et al. [21] also reported that the rate of response to TAI with epirubicin-Lipiodol emulsion (a mixture of 20–30 mg/body epirubicin and 2–4 ml Lipiodol) for advanced HCC was 23%. Our regimen is a mixture of 60 mg/m^2 (median 100 mg/body) epirubicin and 6 ml Lipiodol, which are higher doses than those in the previous studies. In the present study, however, the response rate was only 5%, which was markedly lower than in previous studies. One possible explanation for this difference in the response rate might be the difference in the patients who were enrolled. The patients enrolled in the previous studies had untreated HCC, whereas those in our study had TAE-refractory HCC. When HCC tumors become refractory to TAE, they might acquire resistance to anticancer agents.

Since most HCC patients have underlying cirrhosis, they usually have pancytopenia. Patients with HCC who undergo chemotherapy are therefore more likely to experience severe myelosuppression than patients with other malignant diseases. In this study, 13 (65%) patients developed grade 3–4 neutropenia and 6 (35%) developed grade 3–4 leukocytopenia. The incidence of these hematological toxicities was higher than those reported previously [20]. However, febrile neutropenia was observed in only three patients, and was soon resolved. Among non-hematological toxicities, grade 3 elevation of serum transaminases was frequently observed, although liver function returned to the initial level within 2 weeks after this treatment. The adverse effects of this treatment were not generally serious, and were considered to be moderate.

TAI with epirubicin-Lipiodol emulsion appears to have only modest activity and moderate toxicity when used for the treatment of patients with TAE-refractory HCC, because the response rate (5%) was low and progression-free survival (median 1.1 months) was extremely short. These findings do not support its use in practice, and further studies with the same regimen in patients with TAE-refractory HCC are not recommended. To explore innovative approaches for TAE-refractory HCC, future investigations for treatment with more potent antitumor effects and lower toxicity are warranted.

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