Transcatheter Arterial Infusion Chemotherapy with a Fine-powder Formulation of Cisplatin for Advanced Hepatocellular Carcinoma Refractory to Transcatheter Arterial Chemoembolization

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Objective: The aim of this study was to assess the safety and efficacy of transcatheter arterial infusion chemotherapy using a fine-powder formulation of cisplatin for patients with advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization.

Methods: We retrospectively examined the data of 84 consecutive patients with transcatheter arterial chemoembolization-refractory hepatocellular carcinoma who underwent transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin. Cisplatin was administered at the dose of 65 mg/m² into the feeding artery of the hepatocellular carcinoma. The treatment was repeated every 4–6 weeks, until the appearance of evidence of tumor progression or of unacceptable toxicity.

Results: Of the 84 patients, one patient (1.2%) showed complete response and two patients (2.4%) showed partial response, representing an overall response rate of 3.6% (95% confidence interval, 0.7–10.1). Of the remaining, 38 patients (45.2%) showed stable disease and 41 (48.8%) showed progressive disease. The median overall survival, 1-year survival rate and median progression-free survival in the entire subject population were 7.1 months, 27% and 1.7 months, respectively. Major Grade 3 or 4 adverse events included thrombocytopenia in 12 patients (14%) and elevation of the serum aspartate aminotransferase in 33 patients (39%). The gastrointestinal toxicities were mild and reversible.

Conclusions: Transcatheter arterial infusion chemotherapy using a fine-powder formulation of cisplatin appears to have only modest activity, although the toxicity was also only mild, in patients with transcatheter arterial chemoembolization-refractory hepatocellular carcinoma.

Key words: hepatocellular carcinoma – transcatheter arterial infusion chemotherapy – cisplatin – transcatheter arterial chemoembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is treated by one or more of a wide variety of treatment options available, depending on the tumor characteristics, including the number and size of tumors, and the presence/absence of tumor thrombosis and extrahepatic metastases (1,2). In patients with early-stage HCC, curative therapies can be applied, including resection, liver transplantation or local ablation therapy. However, the prognosis of patients with HCC is still unsatisfactory, mainly because of the high frequency of recurrence post-therapy (3–9). Transcatheter arterial chemoembolization (TACE) has been performed for unresectable advanced HCC in patients who are unsuitable candidates for local ablation therapy or surgical treatment. To date, nine randomized control trials...
PATIENTS AND METHODS

PATIENTS AND TREATMENT

From July 2004 to September 2008, 84 consecutive patients with TACE-refractory HCC underwent TAI using cisplatin at the National Cancer Center Hospital, Tokyo, or the National Cancer Center Hospital East, Chiba, Japan. TACE-refractory tumors were defined as those showing an increase in size or <25% reduction in size of the hypervascular lesions visualized on dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) at 1 month after TACE (30).

TAI was performed by introducing a catheter into the proper, right or left hepatic artery, or another feeding artery by the Seldinger technique, and injecting cisplatin at the dose of 65 mg/m² over 20–40 min. Until the appearance of evidence of tumor progression and/or of unacceptable toxicity, the treatment was repeated every 4–6 weeks for up to six cycles. Antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist (granisetron 1 mg) plus dexamethasone 8 mg was used at the physician’s discretion. Patients received adequate hydration for protection against cisplatin-induced renal dysfunction, and the urine output was carefully monitored, especially during the first 3 days after intra-arterial administration of cisplatin, and intravenous furosemide was administered if the output was judged to be inadequate. In principle, the cisplatin dose was reduced if the patient’s creatinine clearance decreased to below 50 ml/min.

This retrospective study was conducted with the approval of the Institutional Review Board of the National Cancer Center and conducted in accordance with the ethical principles stated in Japanese ethics guidelines for epidemiologic studies.

RESULTS

PATIENT CHARACTERISTICS

The baseline characteristics of the 84 patients enrolled in this study are shown in Table 1. The diagnosis of HCC was made either by histologic examination (44 patients, 52%), or distinctive findings on CT, MRI and/or angiography associated with elevated serum levels of α-fetoprotein or protein induced by vitamin K antagonist II (40 patients, 48%). Of the total, 42 patients each were classified as the Child–Pugh classes A and B, whereas there were no patients of the Child–Pugh class C. Twenty-six patients (31%) had tumor thrombosis in the main and/or first portal vein. Prior therapies other than TACE were hepatectomy (37 patients, 44%), local ablation therapy (33 patients, 39%), TAI (13 patients, 15%) and systemic chemotherapy (10 patients, 12%) with non-platinum-containing regimens. The median number of

(RECTs) of transcatheter arterial embolization or TACE versus best supportive care have been reported (10–18). Three of these RCTs and two meta-analyses have demonstrated a survival benefit of this treatment modality in HCC patients (10,16,17,19,20). On the basis of these results, TACE has been the most commonly employed treatment modality in patients with unresectable advanced HCC, especially those with intermediate-stage disease, who are unsuitable candidates for local ablation therapy (21). However, unfortunately, the disease eventually progresses to becoming refractory to TACE.

Transcatheter arterial infusion chemotherapy (TAI) could be expected to have better antitumor efficacy and lesser toxicity than systemic chemotherapy, because it is associated with only a local increase in the concentrations of anticancer drugs, and therefore, a lower incidence of systemic adverse effects. The reported response rates to TAI with a single agent vary in the range of 9–33% (22–25), and those to TAI using combination regimens vary in the range of 44–73% (26–29). Thus, TAI has high antitumor activity and is widely used in clinical practice, especially in Japan, although no survival benefit has been established yet, because no randomized studies of TAI have been conducted until date.

Cisplatin for Intra-arterial Injection (IA-call®, Nippon Kayaku Co., Ltd) is a powder formulation and represents an improvement over the standard liquid type of cisplatin formulation for intra-arterial administration. Since the solubility of this agent is 2.86 times higher than that of standard cisplatin, the injection time can be shortened. In a clinical study of this agent for advanced HCC, a favorable tumor response rate of 33.8% was reported (25), and this agent was approved for use as an agent for advanced HCC, a favorable tumor response rate of 73% (26–29). Thus, TAI has high antitumor activity and is widely used in clinical practice, especially in Japan, although no survival benefit has been established yet, because no randomized studies of TAI have been conducted until date.

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RESPONSE AND TOXICITY EVALUATIONS

The antitumor effect was evaluated by dynamic CT and/or MRI performed 1 month after each treatment cycle, and after the completion of six cycles, follow-up examinations were performed every 1–3 months. Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (31). The best overall response was recorded for each patient. Progression-free survival was defined as the interval between the date of the initial TAI treatment using cisplatin and either the date of documentation of disease progression (either radiologic or symptomatic progression) or the date of death owing to any cause. Overall survival was measured from the date of the initial TAI treatment using cisplatin to the date of death or last follow-up. Survival curves were estimated using the Kaplan–Meier method. Toxicities were assessed using the Common Terminology Criteria for Adverse Events, version 3.0. Statistical analyses were performed using Dr SPSS II (SPSS Japan Inc., Tokyo, Japan).
previous sessions of TACE was 4 (range 1–17), and the median period from the first TACE to the date on which the tumors were judged to be TACE-refractory was 15.8 months (range 1.0–78.0). The anticancer agents used for the previous TACE sessions were epirubicin in 79 patients, Adriamycin in 17 patients, and mitomycin C in 5 patients.

**TREATMENT DELIVERY AND EFICACY**

In total, 167 cycles of TAI were administered to the 84 patients, with a median of one cycle (range 1–7) per patient. The median cisplatin dose per treatment session was 100 mg (range 50–135). A total of 83 patients received the standard dose of cisplatin in the first session, and the remaining one patient required a 50% reduction in the dose of cisplatin even from the first treatment cycle because of pre-existing renal dysfunction.

Of the study population, one patient showed complete response and two showed partial response, representing an overall response rate of 3.6% [95% confidence interval (CI), 0.7–10.1]. Stable disease was noted in 38 patients and progressive disease in 41 patients. The remaining two patients were not evaluable as they were lost to follow-up. After treatment discontinuation, 50 (60%) patients received supportive care only, 32 (38%) received additional anticancer therapy and 2 (2%) were lost to follow-up. The additional anticancer therapies were TACE with epirubicin or mitomycin C in 18 patients, TAI using non-platinum drugs in 7 patients (including 5-fluorouracil with systemic interferon in 3 patients, epirubicin in 3 patients, and zinostatin-stimalamer in 1 patient), systemic chemotherapy in 5 patients (including S-1, i.e., a mixture of tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate, in 3 patients, and uracil-tegafur plus mitoxantrone in 2 patients), and immunotherapy in 2 patients. By the time of the analysis, except for eight patients who were still alive but showed disease progression, all of the patients had died. The median progression-free survival was 1.7 months (95% CI, 1.1–2.3) and the median overall survival was 7.1 months (95% CI, 4.9–9.3), with a 1-year survival rate of 27% (Fig. 1).

**ADVERSE EVENTS**

Data of all 84 patients were analyzed for adverse events. The adverse events are summarized in Table 2. In regard to the hematologic adverse events, thrombocytopenia was the most common, with 12 (14%) patients developing Grade 3 or 4 thrombocytopenia; however, none of the patients required platelet transfusions. Grade 3 or 4 leukopenia and neutropenia occurred in only 6 and 4% of the patients, respectively. There were no events of febrile neutropenia.

The main non-hematologic adverse events were elevation of the serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT). Grade 3 or 4 elevation of the AST and ALT was observed in 33 (39%) and 5 (6%) patients, respectively. Gastrointestinal adverse events, such as nausea, vomiting, and anorexia, were frequently observed after intra-arterial administration of cisplatin, but most were transient and manageable with appropriate medical treatment, such as antiemetic drug administration and intravenous hydration. There was no serious renal toxicity. Four patients died within 30 days of the last treatment session: two of disease progression, one of acute coronary syndrome,
DISCUSSION

In the current study, the response rate to TAI using cisplatin was only 3.6% in patients with TACE-refractory HCC. Moreover, the median progression-free survival of only 1.7 months was extremely disappointing. The efficacy of TAI using cisplatin for advanced HCC limited to TACE-refractory tumors was much worse than that reported from a previous Phase II study in patients with advanced HCC (response rate, 33.8%) (25). One possible explanation for this discrepancy in the response rate may be the differences in the characteristics of the enrolled patients between the two studies. Most patients in the previous Phase II trial were TACE-naïve, whereas only patients with TACE-refractory disease were included in the current study. In our previous study (30), TAI using epirubicin was reported to have unfavorable efficacy in a subset of patients with TACE-refractory HCC (response rate, 5%). When HCC is treated by TACE and/or becomes resistant to TACE, it might acquire resistance to cytotoxic agents, such as cisplatin or epirubicin. Furthermore, to select suitable candidates for this treatment, the predictive factors for disease control and survival for more than 12 months were also investigated, but could not be clarified (data not shown). Therefore, TAI using cisplatin or epirubicin cannot be recommended at present for this patient population in clinical practice.

Recently, systemic chemotherapy has become an important treatment modality for advanced HCC, because two RCTs (the SHARP trial and the Asia-Pacific trial) of sorafenib versus placebo demonstrated significantly improved time-to-progression and overall survival in the drug-treated group, although sorafenib yielded a far-from-satisfactory response rate of only 2.3–3.3% (33,34). On the basis of the results of these RCTs, sorafenib is acknowledged as a standard agent for systemic chemotherapy in patients with advanced HCC. The efficacy of sorafenib for advanced HCC refractory to TACE has not yet been clarified, but in both of the aforementioned studies, the results of exploratory subgroup analyses in patients treated previously by TACE were reported. In the subset of patients with a previous history of treatment by TACE in the SHARP trial, the disease control rate (DCR) was significantly greater in the patients who were treated with sorafenib (44.2%) than in those who had received placebo (34.4%) (35). In addition, a trend towards a beneficial effect of sorafenib was also observed in relation to the median overall survival in this subgroup of patients \{11.9 vs. 9.9 months [hazard ratio (HR), 0.75; 95% CI, 0.49–1.14]\}. In the Asia-Pacific trial, 41% of the enrolled patients had a previous history of undergoing TACE. The DCR for sorafenib (24.6%) in these patients was higher than that for placebo (9.1%) (36). Moreover, a tendency [HR for death was 0.84 (95% CI, 0.52–1.36)] towards favorable overall survival was also noted in the HCC patients with a previous history of TACE treated with sorafenib when compared with that in the same subgroup of patients who received placebo. Sorafenib appeared to benefit patients with
advanced HCC, regardless of whether or not they had previously been treated by TACE. Thus, molecular-targeted agents, including sorafenib, which exhibit mechanisms of action different from those of cytotoxic agents, may be superior for the treatment of HCC refractory to TACE. Therefore, patients with TACE-refractory HCC are receiving new molecular-targeted agents in clinical trials, and sorafenib is used as the standard agent for the treatment of advanced HCC in clinical practice.

In the current study, the most common Grade 3 and 4 adverse events were elevated AST, thrombocytopenia and anemia, which frequently also reflected the underlying cirrhosis. In terms of the gastrointestinal toxicities, only 4% of the patients experienced Grade 3 anorexia and nausea, and the symptoms resolved within a few days. Thus, the gastrointestinal toxicities were mild and manageable in the current study. There was no need for dose reduction or discontinuation of cisplatin on account of development of toxicities, except in one patient each with Grade 2 elevation of the serum creatinine and Grade 2 fatigue. Thus, advanced HCC patients showed good overall tolerability to TAI using cisplatin, which has also been reported to show favorable efficacy in these patients (25); in our study confined to TACE-refractory patients, however, the treatment showed only modest antitumor activity. TAI using cisplatin may therefore be easy to administer in combination with some molecular-targeted agents, such as sorafenib, since its toxicity is generally mild and its toxicologic profile is distinct from that of sorafenib.

In conclusion, TAI using cisplatin appeared to have only modest activity against TACE-refractory HCC, although this treatment was feasible and well tolerated. Further development of novel treatments is necessary to improve the prognosis of patients with TACE-refractory HCC.

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Conflict of interest statement

None declared.

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