Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

Analysis of 48 Cases

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BACKGROUND. The prognosis of patients with hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is extremely poor. The aim of this study was to elucidate the efficacy of hepatic arterial infusion chemotherapy (HAIC) for patients with advanced HCCs.

METHODS. Forty-eight HCC patients with PVTT were treated by HAIC via a subcutaneously implanted injection port. Of these, 14 had PVTT in the second portal branch and 34 patients had PVTT in the first portal branch or in the main portal trunk. One course of chemotherapy consisted of daily cisplatin (7 mg/m^2 for 1 hour on Days 1–5) followed by 5-fluorouracil (170 mg/m^2 for 5 hours on Days 1–5). Patients were scheduled to receive four serial courses of HAIC. Responders were defined as having either a complete response (CR) or partial response (PR) and nonresponders were defined as exhibiting stable disease or progressive disease.

RESULTS. Following HAIC, 4 and 19 patients exhibited a CR and PR, respectively (response rate = 48%). The 1, 2, 3, and 5-year cumulative survival rates of 48 patients treated with HAIC were 45%, 31%, 25%, and 11%, respectively. Median survival periods for 23 responders and 25 nonresponders were 31.6 (range, 8.3–76.9) months and 5.4 (1.9–29.0) months, respectively. Therapeutic effect (P < 0.001) and hepatic reserve capacity (P = 0.021) were identified as significant prognostic factors by univariate analysis. Multivariate analysis identified only therapeutic effect as being significantly related to survival.

CONCLUSIONS. HAIC using low-dose cisplatin and 5-fluorouracil may be a useful therapeutic option for patients with advanced HCC with PVTT. HCC patients with PVTT who respond to HAIC could certainly have survival benefits.

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KEYWORDS: hepatocellular carcinoma, tumor thrombosis, hepatic arterial infusion chemotherapy (HAIC), prognosis, biochemical modulation, cytoreduction.

The incidence of hepatocellular carcinoma (HCC) has increased during the past decade and HCC has become the leading cause of death among patients with cirrhosis. 1–2 Recent technologic advances in imaging modalities and therapeutic procedures have facilitated early diagnosis and curative treatment in patients with HCC. 3–17 Despite this marked progress in medical science, the prognosis for HCC patients remains unsatisfactory. Surgical resection or liver transplantation for these patients is limited due to coexistent cirrhosis or the limited availability of suitable donor livers. 10–12 Furthermore, HCC
has a high recurrence rate even after “curative” surgery and these tumors progress to an advanced stage. The survival rates of patients with advanced HCC, with complications such as portal vein tumor thrombosis (PVTT) or distant metastasis, remains extremely poor. Previous studies have reported that patients with diffuse HCC involving PVTT survive only 1–2 months if effective treatment is not administered. For patients with advanced HCCs, an effective therapy that maintains a satisfactory quality of life is required. Surgery is considered the most effective treatment in HCC patients with PVTT, although the number of suitable cases is limited because of dissemination of the tumor throughout the liver or coexistence of cirrhosis. Transcatheter arterial embolization (TAE), systemic chemotherapy, hormonal therapy, and interferon (IFN) therapy have been used in patients with advanced HCC, although no survival benefit for these modalities has been reported in various randomized controlled trials (RCT).

Advances in the biotechnology of implantable drug delivery systems have facilitated repeated arterial infusion of chemotherapeutic agents. Hepatic arterial infusion chemotherapy (HAIC) with several anticancer agents, using combinations of obstructive agents and antiproliferative agents, provide a useful option for patients with advanced HCC. We have reported the usefulness of HAIC using low-dose cisplatin and 5-fluorouracil (5-FU) in patients with advanced HCC. The aim of this study was to elucidate the efficacy of this therapy by analyzing the clinical results of 48 HCC patients with PVTT treated in this manner.

**MATERIALS AND METHODS**

**Patients**

From April 1, 1990 to March 31, 2000 at the Department of Medicine II, Kurume University School of Medicine, and its affiliated hospitals, 142 patients with unresectable HCC underwent HAIC using low-dose cisplatin and 5-FU, via a subcutaneously implanted injection port. Due to the progression of HCC or coexisting cirrhosis, these patients were not suitable candidates for either surgical resection or nonsurgical treatments, including microwave coagulation therapy (MCT), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), or TAE. Of the initial 142 patients, 48 with PVTT were enrolled in the current study. Informed consent was obtained from all patients before commencement of the study. The diagnosis of HCC was made by histopathology and/or imaging studies. Of these 48 patients, 7 were confirmed histopathologically and 41 were confirmed clinically using imaging studies, consisting of ultrasonography (US), computed tomography (CT) scan, angiography, and magnetic resonance imaging, and/or high plasma levels of tumor markers such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP). Recent studies have reported the usefulness of serum DCP levels at initial treatment for detecting the development of PVTT. The presence of PVTT was confirmed in all cases by demonstration of one of the following: 1) a low-attenuation intraluminal mass that expanded the portal vein or portal branch on US or enhanced CT scan; 2) the “thread-and-streaks” sign or arterioporal shunts on hepatic angiography; or 3) filling defects in the portal vein or in the portal branch on an indirect portogram obtained from a venous phase angiogram of the superior mesenteric artery.

Table 1 summarizes the clinical profile of 48 HCC patients with PVTT treated by HAIC. They included 41 males and 7 females with an average age of 64.7 years.

**TABLE 1 Clinical Profile of 48 Patients with Hepatocellular Carcinoma**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Tumor characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>41/7</td>
</tr>
<tr>
<td>Age (younger than 65 yrs/66 yrs and older)</td>
<td>27/21</td>
</tr>
<tr>
<td>HCV (+/-)</td>
<td>46/2</td>
</tr>
<tr>
<td>T-bilirubin (mg/dL; mean ± SD)</td>
<td>1.24 ± 0.74</td>
</tr>
<tr>
<td>Albumin (g/dL; mean ± SD)</td>
<td>3.52 ± 0.44</td>
</tr>
<tr>
<td>Child (A/B/C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19/22/7</td>
</tr>
<tr>
<td>Previous treatment (yes/no)</td>
<td>29/19</td>
</tr>
<tr>
<td>Plasma concentration of AFP (&lt; 1,000 ng/mL ± 1/1,000 ng/mL)</td>
<td>21/27</td>
</tr>
<tr>
<td>Plasma concentration of DCP (&lt; 1,000 mAU/mL ± 1/1,000 mAU/mL)</td>
<td>23/25</td>
</tr>
</tbody>
</table>

Tumor location (uni/lobular/bilobular) 12/36
Macroscopic finding (nodular/infiltrative) 12/36
Maximum tumor size (< 50 mm/≥ 50 mm) 12/36
Tumor extent (E1/E2/E3/E4)<sup>b</sup> 3/17/16/12
Tumor stage (1/2/3/4) 0/0/4/44
Grade of portal invasion (Vp1/Vp2/Vp3)<sup>c</sup> 0/14/34
Completion of protocol (yes/no) 40/8


<sup>a</sup> Child stage.<sup>39</sup>
<sup>b</sup> Tumor extent.<sup>20</sup> Tumor replacement of liver parenchyma: E1, < 20%; E2, 20–40%; E3, 40–60%; E4, > 60%.
<sup>c</sup> TNM classification.<sup>34</sup>
<sup>d</sup> Portal invasion.<sup>22</sup> Vp1: in the first or more of the peripheral branch; Vp2: in the second branch; Vp3: in the first branch or trunk.
(range, 49–79 years). Forty-five patients were infected with hepatitis C virus (HCV), one patient was infected with both HCV and hepatitis B virus (HBV), and the remaining two patients were not infected with either HCV or HBV. Twenty-nine patients had a history of treatment of HCC with surgery, PEI, MCT, TAE and/or chemolipiodolization. PVTT grading and tumor extent rating were determined according to the criteria of the Liver Cancer Study Group of Japan.33 PVTT grading was based on the location of the tumor thrombus in the peripheral portal vein: Vp1, tumor thrombus in a third or more of the peripheral branch of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in the first branch or trunk of the portal vein. Tumor extent rating was determined by imaging studies. The rating system was based on the percentage of the tumor extent (E): E1, less than 20% of the whole liver; E2, 20–40% of the whole liver; E3, 40–60% of the whole liver; E4, greater than 60% of the whole liver. Tumor stage was graded according to the TNM classification.34

**Technique of Catheter Placement**

The catheter was inserted through the femoral artery using the Seldinger method. After detection of HCC, an indwelling 4 or 5-Fr catheter was sited. The tip of the catheter was placed at the common hepatic artery or proper hepatic artery. The other end of the catheter was connected to the injection port and the device was implanted in a subcutaneous pocket in the right lower abdominal quadrant.30 The gastroduodenal artery and the right gastric artery were occluded using steel coils to prevent gastroduodenal injury from anticancer agents. The entire procedure was performed under local anesthesia.26,27,30 To prevent occlusion of the catheter, 5 mL (5000 U) of heparin solution was infused biweekly via the injection port.

**Chemotherapeutic Regimen**

After insertion of the drug delivery system in situ, patients received repeated arterial infusion of chemotherapeutic agents via the injection port. One course of chemotherapy consisted of daily administration of cisplatin (7 mg/m² on Days 1–5) followed by 5-FU (170 mg/m² on Days 1–5). Days 6 and 7 were rest days. Both cisplatin and 5-FU were administered by a mechanical infusion pump set at 1 and 5 hours, respectively.30 In principle, patients were to receive four serial courses of chemotherapy and these patients were considered to have had "completion" of HAIC. Patients whose chemotherapy was suspended before the completion of the four serial courses because of adverse reactions or complications were considered to have had "incompletion" of HAIC. One or 2 months after the completion of the initial four courses of HAIC, the patients were to receive a supplemental two to four courses of chemotherapy based on tumor response, performance status, hepatic function, adverse reactions, and complications. The serotonin antagonist ondansetron hydrochloride was administered intravenously as an antiemetic. A saline infusion (500 mL) was administered during chemotherapy.

**Response Criteria**

Local response to treatment was classified following the World Health Organization criteria.35 Complete response (CR) is the complete disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart. Partial response (PR) is a greater than 50% reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart. Stable disease (ST) does not qualify for CR/PR or progressive disease (PD). PD is a greater than 25% increase in the size of one or more measurable lesions or the appearance of new lesions.

**Additional Therapy**

Additional therapies were designed on the basis of performance status, hepatic reserve capacity, tumor responses to HAIC, adverse reactions, and complications. Before January 1996, all patients were followed up without additional therapies until recurrent HCC was detected. After January 1996, patients received additional therapies. For example, patients whose residual tumors were relatively small and localized with disappearance of PVTT received radical local therapies such as surgery, RFA, MCT, and PEI as cytoreduction therapy36,37 and patients who were unsuitable candidates for local therapy received interventional radiology on an outpatient basis (additional chemotherapy). The protocol for additional chemotherapy included weekly HAIC with cisplatin and 5-FU (cisplatin 7 mg/m²/day and 5-FU 170 mg/m²/day, weekly or biweekly), weekly HAIC with cisplatin (cisplatin 7 mg/m²/day, weekly or biweekly), weekly HAIC with epirubicin (epirubicin 7 mg/m²/day, weekly or biweekly), monthly chemolipiodolization with epirubicin (epirubicin 14–20 mg/m²/day with lipiodol 3 mL, monthly), and monthly chemolipiodolization with carboplatin (carboplatin 100 mg/m²/day with lipiodol 3 mL, monthly).

**Statistical Analysis**

Baseline data for patients were expressed as mean ± SD or as medians and ranges. Univariate analysis to identify predictors of survival was performed by the Kaplan–Meier method38 and compared by the log rank...
test. Fifteen variables were assessed, including gender, age (younger or older than 65 years), presence of hepatitis-C antibody (HCV-Ab), hepatic reserve capacity (Child A, B, or C classification), presence of pre-therapy of HCC, AFP levels (< 1000 or > 1000 ng/mL), DCP levels (< 1000 or > 1000 mAU/mL), tumor location (unilobular, bilobular), maximum tumor size (< 50 or > 50 mm), tumor extent (E1, E2, E3, or E4), tumor stage (T3, T4), macroscopic findings (nodular, infiltrative), PVTT rating (Vp2 or Vp3), therapeutic effect after HAIC (responders, nonresponders), and completion of protocol. The multivariate analysis was investigated by the Cox proportional hazard model. Survival was confirmed up to April 30, 2001. Statistical significance was defined as a P value less than 0.05.

RESULTS
Response to Therapy
Patients received 1.8–8.0 (median, 4.0) courses of chemotherapy. HAIC was delivered over more than four serial courses in 40 patients (completion of protocol) and it was suspended in 8 patients within four serial courses (incompletion of protocol). Of the 48 patients, 4 (8%), 19 (40%), 14 (29%), and 11 (23%) patients exhibited CR, PR, ST, and PD, respectively (response rate [CR and PR/ST and PD] = 48%). Of the 19 PR patients, 4 patients had residual tumors which were recognized as necrotic areas.

Additional Therapy
Twenty-two patients were treated with HAIC after January 1996. Of these, 13 patients received additional therapies. One patient was treated with MCT after a marked decrease in the size of HCC and disappearance of PVTT had been achieved by HAIC. Twelve patients underwent additional chemotherapy after HAIC: two patients received weekly HAIC with cisplatin and 5-FU, five patients received weekly HAIC with cisplatin, one patient received weekly HAIC with epirubicin, three patients received monthly chemolipiodolization with epirubicin, and one patient received monthly chemolipiodolization with carboplatin. Of 13 patients, 4 exhibited disappearance of viable HCC after additional therapy: 1 patient was treated with MCT after HAIC and 3 patients were treated with additional chemotherapy (1 treated with weekly HAIC with cisplatin and 5-FU, 2 treated with HAIC with cisplatin). All four cases had exhibited PR after HAIC. Following the additional therapies, 12 (25%) of 48 patients (4 CR patients, 4 PR patients with necrotic tumor, and 4 PR patients who had effective additional therapies) exhibited disappearance of viable HCC.

Survival and Prognostic Factors
The cumulative survival of 48 patients is shown in Figure 1. The 1, 2, 3, and 5-year cumulative survival rates of the 48 patients were 45%, 31%, 25%, and 11%, respectively. The median survival duration of 48 patients treated with HAIC was 10.2 (range, 1.9–76.9) months.

Two of the 15 factors analyzed by univariate analysis showed prognostic significance: Child stage (P = 0.021) and therapeutic effect (P < 0.001; Table 2). Tumor extent and PVTT grading were not significant prognostic factors. Multivariate analysis showed only one variable, therapeutic effect, to be an independent predictor of mortality (P < 0.001).

The median survival times in 23 responders and 25 nonresponders were 31.6 (range, 8.3–76.9) months and 5.4 (range, 1.9–29.0) months, respectively. Of 23 responders, the 1, 2, 3, and 5-year cumulative survival rates of 12 patients with disappearance of viable HCC were 100%, 91%, 81%, and 40%, respectively. The 1, 2, 3, and 5-year disease-free survival rates of 12 patients were 75%, 50%, 50%, and 8%, respectively.

Adverse Reactions and Complications
Table 3 shows the adverse reactions and complications in 48 patients treated with HAIC. The most common adverse reaction was nausea and loss of appetite (35%). Most of these adverse reactions were controllable by medical treatment and/or suspension of HAIC. However, deterioration of liver function forced
the discontinuation of HAIC in four patients and led to death due to irreversible liver dysfunction in one patient.

Complications related mainly to technical problems associated with the indwelling catheter. The majority of patients with these technical problems continued HAIC after implantation of another catheter. Infection around the catheter (sepsis) occurred in two patients: one patient continued HAIC after reimplantation of another catheter and the other patient died of infection caused by methicillin-resistant *Staphylococcus aureus*. Hepatic artery occlusion, which interfered with continuation of HAIC, occurred in one patient.

**Cause of Death**

Ten patients were still alive during the observation period and 38 patients had died. Twenty-three patients (61%) had died of cancer-related disease. Of these, 21 patients (56%) had died of tumor extension and 2 patients (5%) had died of tumor rupture. Eight patients (21%) had died of gastrointestinal bleeding and four patients (10%) had died of liver failure, including one patient who died of liver injury associated with HAIC. Three patients (8%) died of other causes, including sepsis due to catheter infection (one), pneumonia (one), and cerebral bleeding (one).

**DISCUSSION**

HCC is associated with a high risk of portal vein involvement, which is reportedly observed in 64.7% of cases at autopsy. PVTT is an important prognostic factor in patients with HCC and multivariate analyses have shown it to be a significant clinicopathologic variable that influences survival. However, this vascular involvement is generally refractory to treatment. Surgery is considered the most effective treatment in HCC patients with PVTT. Fujii et al. reported the efficacy of surgical treatment in HCC patients with PVTT. In 104 patients with HCC with PVTT, the survival rates in the surgical \( n = 32 \) and nonsurgical groups \( n = 72 \) were 72% and 25% at 1 year, 59% and 9% at 2 years, and 54% and 5% at 3 years \( P < 0.001 \), respectively. However, the number of suitable cases for surgery is limited because of dissemination of the tumor throughout the liver or coexistence of cirrhosis. PEI is indicated when the throm-

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**TABLE 2**

Factors Influencing Cumulative Survival of Patients Analyzed by Univariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>( P ) value</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (males/females)</td>
<td>0.559</td>
<td>Tumor location (unilobular/bilobular)</td>
</tr>
<tr>
<td>Age (younger than 65/65 yrs and older)</td>
<td>0.282</td>
<td>Maximum tumor size (&lt; 50 \text{ mm/kg} \geq 50 \text{ mm/kg})</td>
</tr>
<tr>
<td>HCV-Ab ( r &lt; 1 \text{ } )</td>
<td>0.283</td>
<td>Tumor extent (E1 or E2/E3 or E4)</td>
</tr>
<tr>
<td>Child stage (A/B or C)</td>
<td>0.021</td>
<td>Tumor stage (3/4)</td>
</tr>
<tr>
<td>Previous treatment (present/absent)</td>
<td>0.058</td>
<td>Macroscopic finding (nodular/infiltrate)</td>
</tr>
<tr>
<td>Plasma concentrations of AFP ( &lt; 1,000 \text{ ng/mL} \geq 1,000 \text{ ng/mL} )</td>
<td>0.961</td>
<td>Grade of portal invasion (Vp2/Vp3)</td>
</tr>
<tr>
<td>Plasma concentrations of DCP ( &lt; 1,000 \text{ ng/mL} \geq 1,000 \text{ ng/mL} )</td>
<td>0.373</td>
<td>Therapeutic effect (PR or CR/ST or PD)</td>
</tr>
<tr>
<td>HCV-Ab: hepatitis C virus antibody; AFP: ( \alpha )-fetoprotein; DCP: des-gamma-carboxy prothrombin; Vp: portal vein tumor thrombosis; CR: complete remission; PR: partial remission; ST: stable disease; PD: progressive disease; NS: not significant.</td>
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<td></td>
</tr>
</tbody>
</table>

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**TABLE 3**

Adverse Reactions and Complications Related to HAIC

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>No. of patients (%)</th>
<th>Complications</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, loss of appetite</td>
<td>17 (35)</td>
<td>Obstruction of catheters</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>6 (13)</td>
<td>Hematoma around injection port</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Leukopenia, thrombocytopenia</td>
<td>6 (13)</td>
<td>Infection around catheter (sepsis)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Deterioration of hepatic function</td>
<td>6 (13)</td>
<td>Dislocation of the tip of catheter</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Renal damage</td>
<td>1 (2)</td>
<td>Obstruction of hepatic artery</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Auditory disturbance</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAIC: hepatic arterial infusion chemotherapy.
HAIC for HCC with PVTT/Ando et al.

bus is located segmentally (Vp2) or subsegmentally (Vp1).16 TAE is contraindicated because of the risk of necrosis of the noncancerous portion of the liver and deterioration of the hepatic reserve capacity.17 Liver transplantation is suitable for small HCCs.10 Systemic chemotherapy, hormonal therapy, and IFN therapy are all of limited value and only a few patients benefit from previous therapy.22-24,41 Despite marked progress in medical science and technology, none of the previous therapies has been effective for these patients.

Regional HAIC is a reasonable drug delivery system for patients with advanced HCCs because the tumors derive most of their blood supply from the hepatic artery, whereas the portal vein supplies the normal liver parenchyma.42 HAIC may provide higher concentrations of chemotherapeutic agents to HCCs. Moreover, hepatic extraction of chemotherapeutic agents results in minimal systemic concentrations of these agents, potentially minimizing systemic toxicity.43 In a previous study,30 we reported the usefulness of HAIC with low-dose cisplatin and 5-FU in nine patients with advanced HCC with PVTT. Patt et al.25 reported the usefulness of HAIC with the FLAP regimen, comprising cisplatin, doxorubicin, fluoruridine, and leucovorin. They treated 31 patients with advanced HCC, including 15 patients with PVTT. Fourteen patients had greater than 50% liver replacement of the tumor. The response rate and the median survival duration were 41% and 15 months, respectively. However, patients positive for HBV antigen and/or HCV-Ab showed an increased susceptibility to myelotoxic drugs and median survival duration among these patients was significantly shorter (7.5 months) than among hepatitis nonreactive patients. In an RCT, Chung et al.29 demonstrated the efficacy of adjuvant systemic IFN therapy in HAIC using a cisplatin regimen. The study included 68 patients with advanced HCC with major PVTT or extrahepatic metastasis. The patients were divided into three groups. The first group received combination therapy of IFN and HAIC with cisplatin (n = 19), the second group received HAIC with cisplatin alone (n = 23), and the third group was treated conservatively (n = 26). Their results revealed a significantly higher survival rate among patients in the first group, compared with survival rates among patients in the second and third groups. However, the response rate and median survival duration of the first group were only 27% and 4.8 months, respectively.29 In the current study, the response rate and median survival duration of 48 patients with PVTT were 48% and 10.2 (range, 1.9–76.9) months, respectively. Moreover, 12 patients exhibited disappearance of viable HCC (4 CR patients, 4 PR patients with necrotic tumor, and 4 PR patients who had effective additional therapies). These patients had a favorable result. Their 1, 2, 3, and 5-year cumulative and disease-free survival rates were 100%, 91%, 81%, 40%, and 75%, 50%, 50%, 8%, respectively.

The rationale of this treatment regimen is that cisplatin and 5-FU have an antitumor effect,44,45 cisplatin has a synergistic effect as a modulator for 5-FU,46-48 and cisplatin and 5-FU can be administered in low doses to reduce adverse reactions. This combination is used widely to treat various malignancies, including breast, ovarian, and colorectal carcinoma.46-48 as well as HCC.27,36

Univariate analysis demonstrated that two factors, namely, therapeutic effect (P < 0.001) and hepatic reserve capacity (P = 0.021), influenced the prognosis (Table 2). Patients with Child A cirrhosis were suitable candidates for HAIC using this regimen, irrespective of previous therapy for HCC, high plasma levels of tumor markers, degree of tumor involvement of the liver, and degree of portal vein invasion. Several investigators have reported that the hepatic reserve capacity is an independent prognostic factor in patients with HCC.11,14-20,41 We presume that patients with good hepatic reserve capacity are more tolerant to adverse reactions induced by anticancer agents compared with patients with poor hepatic reserve capacity, thus allowing continuation of HAIC. In the current study, all of the patients with Child A cirrhosis received HAIC for more than four serial courses (completion of HAIC). However, completion of the protocol was not a significant prognostic factor in this study. Multivariate analysis revealed that only the therapeutic effect was an independent prognostic factor of survival. The median survival intervals in 23 responders and 25 non-responders were 31.6 (range, 8.3–76.9) months and 5.4 (range, 1.9–29.0) months, respectively. Llovet et al.20 reported the natural history of patients with untreated nonsurgical HCC and revealed that the median survival duration of patients with PVTT was only 2.4 months. Okuda et al.18 reported similar results. A statistically significant prognostic advantage for HAIC in patients with PVTT should be evaluated by a properly conducted RCT. However, in view of the studies demonstrating that the postdiagnostic median survival period of HCC patients with PVTT was only a few months,18,20 the survival periods of responders in our current study were longer compared with those previously reported. It is noteworthy that the non-responders in our study also exhibited slightly longer median survival intervals than those previously reported,18,20 although most patients in the study (61%) died of cancer-related disease. Starting in January 1996, we administered additional therapies in patients with residual tumors after HAIC. One patient subse-
The toxicity of chemotherapy was a substantial problem in all treatment arms. The most common adverse reactions and complications were early gastrointestinal symptoms and technical problems related to the indwelling catheter. The majority of these problems were resolved by medical treatment or reimplantation of the catheter (Table 3). However, two patients (4%) died of deterioration of hepatic function or catheter-related sepsis and four patients could not continue HAIC due to deterioration of hepatic function. Caution should be exercised in preventing and monitoring adverse reactions or complications, especially with respect to deterioration of hepatic function.

In conclusion, this chemotherapeutic regimen may potentially be a basic protocol for HCC patients with involvement of the portal vein. Patients with PVTT who respond to HAIC could certainly exhibit a basic protocol for HCC patients with preserved hepatic reserve capacity. Therefore, hepatic function should be monitored carefully during administration of HAIC.

REFERENCES


