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CLINICAL TRIAL REPORT

# A randomized comparative study of high-dose and low-dose hepatic arterial infusion chemotherapy for intractable, advanced hepatocellular carcinoma

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**Abstract**
*Purpose* Hepatic arterial infusion chemotherapy (HAIC) has been reported to be effective in patients with advanced hepatocellular carcinoma (HCC).
*Methods* In this multicenter, prospective, open-labeled, clinical trial, we randomly assigned 68 patients with advanced HCC to receive either low-dose [$n = 32$, 5-fluorouracil (FU), 170 mg/m$^2$ and cisplatin, 7 mg/m$^2$ on days 1–5] or high-dose HAIC ($n = 36$, 5-FU, 500 mg/m$^2$ on days 1–3 and cisplatin, 60 mg/m$^2$ on day 2) every 4 weeks via an implantable port system.
*Results* A total of 207 cycles of HAIC was given to the 68 patients. Overall, 6 patients (8.8%) achieved a partial response and 21 patients (30.9%) had stable disease. The objective response rate (CR + PR) was significantly improved in the high-dose group compared to the low-dose group (16.7% vs. 0%, $P = 0.024$). The median time to disease progression and overall survival were slightly prolonged in the high-dose group compared to the low-dose group (median survival, 193 vs. 153 days; $P = 0.108$; median time to disease progression, 145 vs. 90 days; $P = 0.095$). Multivariate analysis showed that tumor response to treatment [$P = 0.007$, RR 2.27 (95% CI, 1.248–4.132)] was the only factor associated with overall survival. All adverse events were tolerable and successfully managed in both treatment groups.
*Conclusions* Both HAIC regimens are safe and effective in patients with advanced HCC. High-dose HAIC achieves a better tumor response compared to low-dose HAIC.

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**Keywords** Hepatocellular carcinoma · Hepatic arterial infusion chemotherapy · High dose · Low dose · 5-Fluorouracil · Cisplatin

## Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide [1]. Prognosis of patients with early stage HCC is relatively good because of the availability of potentially curative therapies that include resection, liver transplantation, or local ablation either with radiofrequency (RF) or percutaneous ethanol injection (PEI). However, these approaches are only suitable in 30–40% of patients in Western countries, and even fewer in Asia [2]. The prognosis of patients with unresectable HCC is poor, with median survival of <1 year. Patients with advanced-stage disease who are left untreated have a median survival of only 6–7 months [3]. Recently, the multitarget tyrosine kinase inhibitor sorafenib was reported to improve median survival in advanced HCC [4] and has become the new standard systemic therapy for such patients. However, in patients with portal vein invasion or extrahepatic metastasis, the effect is significantly diminished.

With the exception of sorafenib, systemic chemotherapy using conventional cytotoxic agents has not been effective in HCC therapy [5, 6]. However, repetitive hepatic arterial infusion chemotherapy (HAIC) with conventional chemotherapeutic agents using an implantable port system has been reported to be a useful therapeutic modality for patients with advanced HCC [7–13]. Compared with systemic chemotherapy, infused chemotherapeutic agents in HAIC can be delivered to the liver at a high concentration and lower toxicity.

Various chemotherapeutic agents have been tried individually or in combination for HAIC treatment of HCC, with 5-fluorouracil (5-FU, a thymidylate synthase inhibitor) and cisplatin (a DNA cross-linking compound) being most commonly used. While various combinations of 5-FU and cisplatin have been investigated for use in HAIC [7, 10, 12–14], few studies have assessed these HAIC regimens comparably in patients with advanced HCC. In this multicenter, prospective, randomized controlled trial, we compared the safety and efficacy of two different HAIC 5-FU + cisplatin regimens in patients with advanced HCC, with the aim of optimizing treatment.

## Methods

### Patients

Patients with intractable, advanced HCC including major portal vein invasion were recruited between January 2006 and January 2008, and were followed until December 2008 in this multicenter prospective study to compare the efficacy and safety of either low-dose or high-dose HAIC every 4 weeks via the implantable port system. The diagnosis of HCC was made either by histopathologic confirmation or typical appearance of HCC on two dynamic imaging examinations, or via one dynamic technique with elevated serum α-fetoprotein (AFP) (>400 ng/ml) [11, 15]. Intractable, advanced HCC was defined as HCC with main portal vein invasion, infiltrative type and/or refractory to surgical resection or nonsurgical intervention (transcatheter arterial chemoembolization, RF ablation and PEI). Eligible patients met the following criteria: aged 18–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, Child–Pugh score of 5 or 6 (<7), preserved organ function (serum creatinine level ≤1.5 mg/dl and aminotransferase ≤5 times the institutional upper limit of normal), acceptable blood cell counts (absolute neutrophil count of ≥1,500 cells/mm$^3$, platelet count ≥75,000 cells/mm$^3$, hemoglobin ≥10 g/dl), and at least one unidimensionally measurable lesion. Patients were ineligible if they had extrahepatic malignancy or extrahepatic metastases, had experienced antitumor therapy within 8 weeks before enrollment, or had any other concurrent serious medical condition(s) that would interfere with participation in the study. The trial was conducted according to the current declaration of Helsinki, and the protocol was approved by the institutional ethics committee of each participating institution. All patients gave informed consent and were randomized.

### Implantation of the arterial port system

For arterial chemoinfusion, an arterial catheter was inserted through the femoral artery. After injection of local anesthetic, the femoral artery was punctured using the Seldinger technique and the catheter was inserted to the celiac trunk. After arteriography and portography was acquired, HCC and its feeding artery were detected and the tip of the Port-A-Cath1 catheter (Deltac, St Paul, MN) was placed at the common hepatic artery or proper hepatic artery under fluoroscopic guidance. Gastroduodenal artery was selectively embolized with a microcoil to prevent reflux of cytotoxic drug to the stomach and duodenum. The peripheral end of the catheter was connected to the port system and the port device was implanted in a subcutaneous pocket in the right or left iliac fossa, as appropriate. Heparin solution (10 ml, 10,000 units, 1:1,000 dilution) was locked into the injection port after each cycle of chemotherapy to prevent occlusion of the catheter. Hepatic angiography was performed with arterial chemoinfusion unless otherwise contraindicated.

### Study drugs and dose modification

All patients in both treatment groups were randomly allocated to receive either high-dose or low-dose HAIC. Both involved 5-FU and cisplatin, which were purchased from Choong-wae (Seoul, South Korea) and Il-dong (Seoul, South Korea), respectively. The high-dose regimen consisted of 500 mg/m$^2$ 5-FU for 5 h on days 1–3 and 60 mg/m$^2$ cisplatin for 2 h on day 2). The low-dose regimen consisted of 170 mg/m$^2$ 5-FU on days 1–5 and 7 mg/m$^2$ cisplatin on days 1–5. Both regimens were conducted every 4 weeks and both were administered via the hepatic artery using the implantable port system. Intravenous hydration was performed to prevent cisplatin-induced nephrotoxicity and prophylactic anti-emetic treatment comprised of 5-hydroxytryptamine-3 antagonists was carried out with all patients. Treatment cycles were repeated as described above and continued until disease progression or unacceptable toxicity was evident, or the patient refused to continue. The dose of each chemotherapeutic agent was adjusted according to the toxicity observed with each treatment cycle. The dose of the subsequent treatment was reduced by 25% when repeated grade 2 or any grade 3 toxicity during the preceding cycle occurred. Treatment was stopped in the case of any grade 4 toxicity. If treatment was delayed for more than 4 weeks, the patient was discontinued from the study.

### Study assessments

Tumor response, especially objective response rate [complete response (CR) plus partial response (PR)] was primarily evaluated. Time to radiologic progression (TTP) and overall survival (OS) was secondarily evaluated. Before the initiation of the first treatment, pretreatment evaluations consisted of medical history, physical examination, laboratory tests (including complete blood count, blood chemistry, virologic marker, serum AFP), chest and abdominal X-ray, and computed tomography (CT) scan or magnetic resonance imaging. During treatment, toxicity assessment, laboratory tests, and chest and abdominal X-rays were repeated every 4 weeks before each treatment cycle. CT scans were performed every two cycles or, if needed to evaluate treatment response or confirm disease progression. Tumor responses were classified according to the World Health Organization criteria modified according to the European Association for the Study of the Liver guideline [16]. TTP was calculated from the initiation of treatment to radiologic disease progression. OS was calculated from the initiation of treatment to death or last follow-up visit. Toxicity assessment was performed for all patients who received at least one cycle of HAIC and evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 3.0).

### Statistical analyses

Continuous data were expressed as medians and ranges, and categorical data as percentages. Treatment response between groups was compared using the Chi-square or Fisher's exact tests. Other variables between different groups were compared using these tests, or independent *t* test, as appropriate. Cumulative survival and progression rates were calculated using the Kaplan–Meier method and the difference between groups were compared by the log-rank test. A Cox proportional-hazards model was used to reveal independent clinical factors or groups affecting overall survival rate. All data was analyzed using SPSS version 14.0 software (SPSS, Chicago, IL).

## Results

### Patient characteristics

A total of 68 patients were enrolled into the study between January 2006 and December 2008. Of these, 36 patients were allocated to the high-dose group and 32 to the low-dose group. The baseline characteristics of all patients are shown in Table 1. The median age was 53 years and 88% of the patients were male. The most common cause of underlying liver disease was hepatitis B virus infection (76.4%) and 91% were Child–Pugh class A. Eighty-eight percent of patients had portal vein tumor thrombosis and 55 (80.8%) patients had a liver tumor burden $\geq$50%. One-third of patients (38%) had received previous treatment for HCC. The baseline characteristics between the two treatment groups were similar (Table 2).

### Clinical efficacy

A total of 207 cycles of HAIC was administered to 68 patients with a mean of three cycles for each patient (range 1–11 cycles). The median dose of cisplatin and 5-FU was 100 mg (range 60–120 mg) and 880 mg (range 500–1,000 mg) $\times$ 3 in the high-dose group and 12 mg (range 10–19.5 mg) $\times$ 5 and 290 mg (range 250–390 mg) $\times$ 5 in the low-dose group at each cycle. During the treatment, dose reduction or treatment delay was observed in 13 patients (seven in the high-dose group and six in the low-dose group, $P = 0.993$). The cumulative total dose of anticancer agents was 75–1,144 mg (347.2 $\pm$ 249.7 mg, median 268 mg) for cisplatin, 1,950–30,393 mg (8,877.1 $\pm$ 6,514.7 mg, median 6,757.5 mg) for 5-FU in high-dose group and 9–180 mg (36.9 $\pm$ 33.7 mg, median 24 mg) for cisplatin, 696–6,600 mg (2,400.8 $\pm$ 1,562.2 mg, median 1,824 mg) for 5-FU in low-dose group.

**Table 1** Baseline characteristics of the enrolled patients

| Characteristics | Number of patients |
|---|---|
| Enrolled patients | 68 |
| Age (years)* | 53 (30–69) |
| Sex | |
| Male/female | 60/8 |
| Causes | |
| HBV/HCV/non-viral | 52/8/8 |
| Child–Pugh class | |
| A/B | 62/6 |
| Staging | |
| III/IVA (UICC) | 9/59 |
| IIIA/IIIB/IIIC (AJCC) | 65/1/2 |
| CLIP score (0/1–3/4–6) | 0/31/37 |
| BCLC stage (B/C) | 8/60 |
| Tumor type | |
| Nodular/massive/infiltrative/noduloinfiltrative | 10/23/31/4 |
| Tumor size (cm) | |
| ≤10/>10 | 28/40 |
| Tumor number | |
| Single/multiple | 8/60 |
| Portal vein thrombosis | 60 |
| Main PV | 20 |
| Rt or Lt PV | 26 |
| Main + Rt or Lt PV | 14 |
| Previous treatment | 25 |
| TAC/TAC + PEI/TAC + OP | 21/1/3 |
| Antiviral treatment | 24 |
| Lamivudine | 17 |
| Entecavir | 7 |
| Platelet count ($\times 10^3$/ml)* | 137.5 (48–526) |
| ALT (IU/L)* | 40 (10–641) |
| Total bilirubin (mg/dl)* | 0.9 (0.3–2.5) |
| PT (INR)* | 1.12 (0.92–1.79) |
| AFP level (ng/ml)* | 1920 (2.7–1,558,000) |

*HBV* hepatitis B virus, *HCV* hepatitis C virus, *PV* portal vein, *Rt* right, *Lt* left, *TAC* transcatheter arterial chemotherapy, *PEI* percutaneous ethanol injection, *OP* operation, *ALT* alanine aminotransferase, *PT* prothrombin time, *AFP* α-fetoprotein

* Expressed as median (range)

**Table 2** Comparison of clinical factors between high-dose group and low-dose group

| | High-dose group ($n = 36$) | Low-dose group ($n = 32$) | *P* value |
|---|---|---|---|
| Age (years)* | 53 (30–69) | 54 (32–69) | 0.717 |
| Sex | | | |
| Male/female | 32/4 | 28/4 | 0.859 |
| Causes | | | |
| HBV/HCV/non-viral | 30/3/3 | 22/5/5 | 0.367 |
| Child–Pugh class | | | |
| A/B | 33/3 | 29/3 | 0.880 |
| Stage | | | |
| UICC (III/IVA) | 5/31 | 4/28 | 0.622 |
| IIIA/IIIB/IIIC (AJCC) | 35/0/1 | 30/1/1 | 0.362 |
| CLIP score (0/1–3/4–6) | 0/18/18 | 0/13/19 | 0.438 |
| BCLC stage (B/C) | 4/32 | 4/28 | 0.859 |
| Tumor size (cm) | | | |
| ≤10/>10 | 11/25 | 17/15 | 0.084 |
| Tumor number | | | |
| Single/multiple | 6/30 | 2/30 | 0.266 |
| Tumor type | | | |
| Nodular/massive/infiltrative/noduloinfiltrative | 3/15/17/1 | 7/8/14/3 | 0.187 |
| Portal vein thrombosis | | | |
| Yes/no | 32/4 | 28/4 | 0.859 |
| Antiviral treatment | | | |
| Yes/no | 13/23 | 11/21 | 0.881 |
| AFP level (ng/ml)* | 1561 | 2134 | 0.467 |
| | (3.2–1558000) | (2.7–185142) | |
| ALT (IU/L)* | 41 (10–641) | 36 (15–135) | 0.515 |
| Total bilirubin (mg/dl)* | 0.9 (0.3–2.5) | 0.98 (0.4–1.9) | 0.313 |
| PT (INR)* | 1.11 (0.92–1.79) | 1.18 (0.93–1.52) | 0.208 |

*HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *ALT* alanine aminotransferase, *PT* prothrombin time

* Expressed as median (range)

Among the 68 patients, 60 were evaluated for the tumor response. The remaining eight patients withdrew from the study before the time of assessment due to port system infection ($n = 1$), progressive liver disease ($n = 5$), and personal decision to withdraw ($n = 2$). On intent-to-treat analysis, PR was observed in six patients (8.8%), SD in 21 (30.9%) and progressive disease (PD) developed in 33 (48.5%). According to the treatment group, PR, SD, and PD were 16.7, 33.3, and 44.4% in the high-dose group and 0, 28.1, and 53.1% in the low-dose group, respectively. All partial response was observed in the high-dose group. The objective response rate (CR + PR) was significantly improved in the high-dose group compared to the low-dose group (16.7 vs. 0%, $P = 0.024$). The disease control rate (CR + PR + SD) was slightly improved in the high-dose group compared to the low-dose group (50 vs. 28.1%, $P = 0.157$). After the treatment, the median AFP level changed from 1,561 to 873 ng/ml in the high-dose group and from 2,134 to 2,849 ng/ml in the low-dose group (Fig. 1).

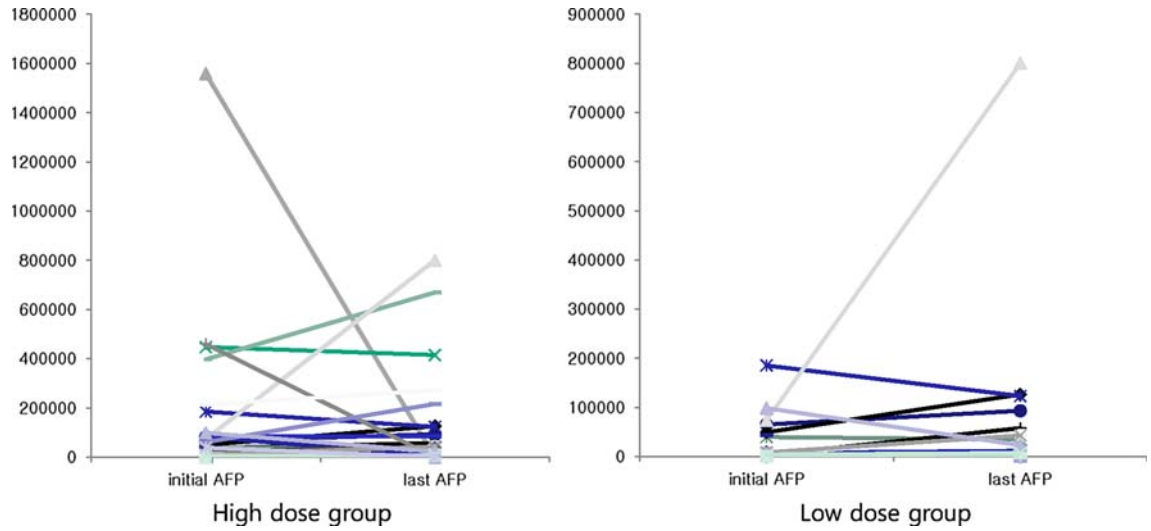


**Fig. 1** Changes in AFP levels before and after high-dose and low-dose HAIC treatment. AFP level did not change significantly after treatment in both treatment group

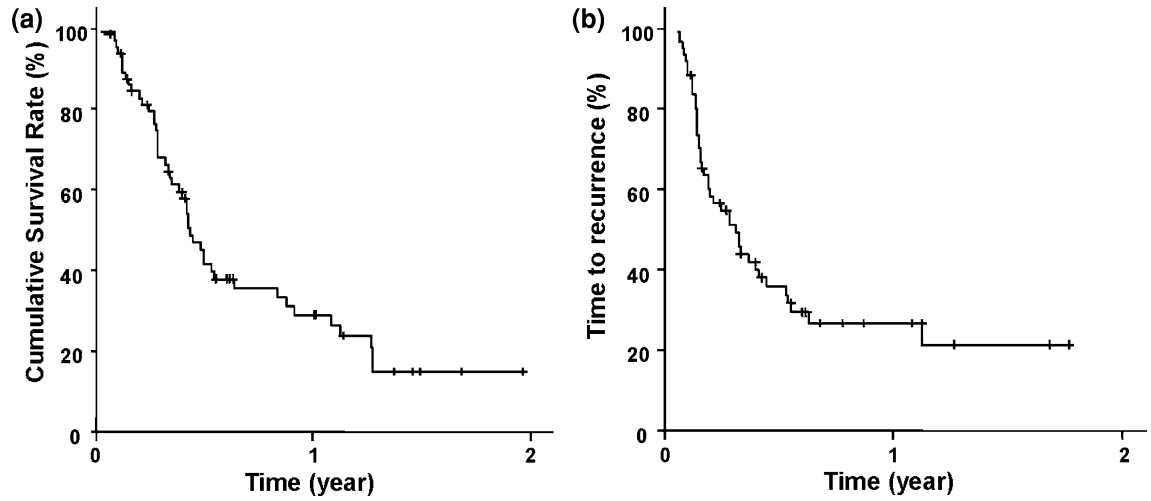


**Fig. 2** **a** OS and **b** TTP in the total enrolled patients

Survival and prognostic factors

In total, the overall survival rate was 32.4% (22/68). The median OS and median TTP was 158 days (95% CI 127–189 days) and 115 days (95% CI 71–158 days) (Fig. 2). The 6-month and 1-year cumulative survival rates were 43.3 and 28.9%, respectively. The median OS and median TTP were 193 days (95% CI 133–252 days) and 145 days (95% CI 90–200 days) in the high-dose group and 153 days (95% CI 114–191 days) and 90 days (95% CI 34–146 days) in the low-dose group, respectively. The OS and TTP were slightly longer in the high-dose group than in the low-dose group, but there was no statistical significance ($P = 0.108$ and $P = 0.095$, respectively) (Fig. 3).

When the factors affecting patient OS were analyzed, pretreatment AFP level, maximum tumor size, CLIP stage, and tumor response to treatment were significantly associated with patient survival on univariate analysis (Table 3). On multivariate analysis, tumor response to treatment [$P = 0.007$, RR 2.27 (95% CI 1.248–4.132)] was independently associated with OS. Any patients with PR did not show tumor progression after achieving PR. Thirty-eight percent (8/21) of patients with SD showed tumor progression and their median TTP was significantly longer than patients with PD ($P = 0.001$). The 1-year survival rates were 83, 37.9, and 16.2% in groups with PR, SD, and PD, respectively ($P = 0.001$) (Fig. 4).

The baseline characteristics were compared among patients showing PR, SD, and PD (Table 4). Significantly, multiple tumor nodules were significantly associated with unfavorable objective tumor response (CR + PR vs. SD + PD, 40 vs. 8%, $P = 0.020$) and maximum tumor size

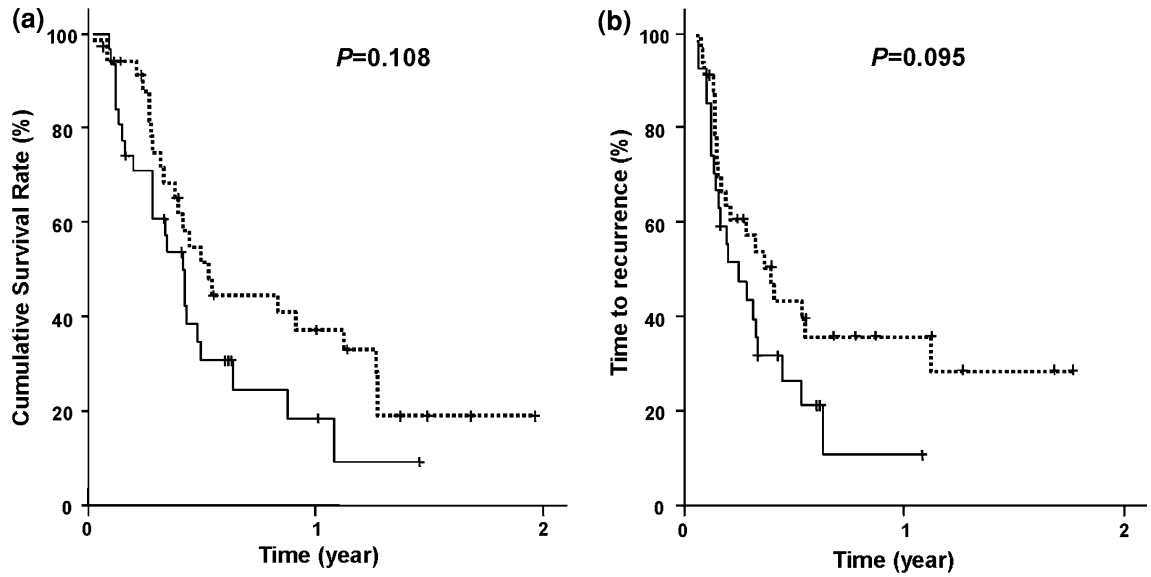


**Fig. 3** Comparison of (**a**) OS and (**b**) TTP in patients undergoing high-dose and low-dose hepatic arterial infusion chemotherapy. OS and TTP were longer in the high dose HAIC group compared with the low-dose HAIC group, although there was no statistical significance. The solid line indicates low-dose HAIC group, dashed line, high dose HAIC group

was more associated with poor disease control rate (CR + PR + SD vs. PD, $10.2 \pm 4.10$ vs. $13 \pm 4.39$ cm, $P = 0.048$).

### Treatment outcome stratified by the etiology of underlying cirrhosis

Among 52 patients with HBV as the etiology of underlying cirrhosis, 20% (6/30) achieved PR and 33% (10/30) was SD in high-dose group, while none showed the objective response and 22.7% (5/22) was SD in low-dose group ($P = 0.040$). Moreover, in this subgroup with HBV, OS and TTP were significantly prolonged in high-dose group compared with low-dose group ($P = 0.016$ and $P = 0.027$, respectively). In patients with either HCV infection or with non-viral cause, none showed PR and treatment response, OS, TTP was not different in both treatment groups.

### Treatment-related toxicity

All treatment-related toxicity and femoral port-related complications in each treatment groups are summarized in Table 5. Overall, 25 (37.3%) patients (14 high-dose patients and 11 low-dose patients, $P = 0.774$) developed more than one adverse symptom or sign during the treatment. The most common toxicity was hepatic and gastrointestinal symptoms. Most adverse events were controllable by medical treatment and/or suspension of HAIC (Fig. 5). However, seven patients (four in the high-dose group and three in the low-dose group) had to discontinue HAIC due to continued deterioration of liver function. Among patients with hematologic toxicity, two experienced dose reduction due to neutropenia, but there was no report of neutropenia-related infection. Among patients with hepatic toxicity, grade 3 toxicity occurred in two patients who ingested herbal medication. These patients had to withdraw from the study due to persistent elevation of liver enzymes.

All femoral ports were successfully implanted. Femoral port occlusion occurred in one patient and was successfully managed by implanting a new port system. Femoral port infection developed in two patients. The port infection was controlled with antibiotics and conservative care, but one patient discontinued HAIC.

## Discussion

The treatment options for intractable, advanced HCC such as HCC with main portal vein invasion, infiltrative HCC, HCC refractory to surgical resection or nonsurgical intervention are very few [16, 17]. Recently, hepatic artery chemoinfusion has been reported to be a useful palliative therapeutic option for patients with advanced HCC. In addition to its effective drug delivery system, HAIC can be applied to HCC with portal vein thrombosis or bilobar involvement. However, the response rates of HCC in the several study published about HAIC are difficult to compare because of disparate chemotherapy regimens and tumor burdens. In this study, two different chemotherapeutic regimens were randomly compared in 68 patients with advanced HCC. Most (88%) of the patients were BCLC stage C. The objective response rate and median OS was

**Table 3** Univariate and multivariate analyses of predictive factor for overall survival

| | Number | Median survival time | *P* value | *P* value | RR (95% confidence interval) |
|---|---|---|---|---|---|
| Sex | | | 0.076 | 0.050 | 0.286 (0.082–1.001) |
| Male | 60 | 155 | | | |
| Female | 8 | 464 | | | |
| Age | | | 0.108 | 0.921 | 1.044 (0.445–2.450) |
| ≤55 years | 41 | 153 | | | |
| >55 years | 27 | 164 | | | |
| Cause | | | 0.238 | | |
| Viral | 60 | 153 | | | |
| Non-viral | 8 | 319 | | | |
| AFP level | | | 0.029 | 0.402 | 1.542 (0.560–4.248) |
| ≤400 ng/ml | 25 | 232 | | | |
| >400 ng/ml | 42 | 127 | | | |
| Antiviral treatment | | | 0.765 | | |
| No | 44 | 160 | | | |
| Yes | 24 | 156 | | | |
| Previous treatment | | | 0.225 | | |
| No | 43 | 180 | | | |
| Yes | 25 | 145 | | | |
| Staging | | | | | |
| CLIP (1–3/4–6) | 31/37 | 304/116 | 0.004 | 0.632 | 1.260 (0.488–3.253) |
| BCLC stage (B/C) | 8/60 | 319/156 | 0.737 | | |
| Maximum tumor size | | | 0.016 | 0.130 | 1.766 (0.847–3.684) |
| ≤15 cm | 55 | 164 | | | |
| >15 cm | 13 | 116 | | | |
| Treatment group | | | 0.166 | 0.993 | 0.997 (0.486–2.046) |
| High dose | 36 | 180 | | | |
| Low dose | 32 | 153 | | | |
| Portal vein thrombosis | | | 0.736 | | |
| No | 8 | 319 | | | |
| Yes | 60 | 156 | | | |
| Tumor number | | | 0.487 | | |
| Single | 8 | 105 | | | |
| Multiple | 60 | 158 | | | |
| Tumor type | | | 0.700 | | |
| Nodular | 10 | 155 | | | |
| Massive | 23 | 193 | | | |
| Infiltrative | 31 | 158 | | | |
| Noduloinfiltrative | 4 | 49 | | | |
| Treatment response | | | 0.001 | 0.007 | 2.27 (1.248–4.132) |
| PR | 6 | NR | | | |
| SD | 21 | 304 | | | |
| PD | 33 | 127 | | | |

*RR* relative risk, *AFP* α-fetoprotein, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NR* not reached

16.7% and 193 days in the high-dose group, and 0% and 153 days in the low-dose group, respectively. In previous studies, HAIC with low-dose cisplatin and 5-FU administered daily 5 days a week for 4 consecutive weeks resulted in a response rate of 44.4–48% and median OS of 10.2–14.9 months [7, 12]. In another study, HAIC with high-dose 5-FU and cisplatin for 3 days every 4 weeks resulted in the objective response rate of 22.0% and median OS of

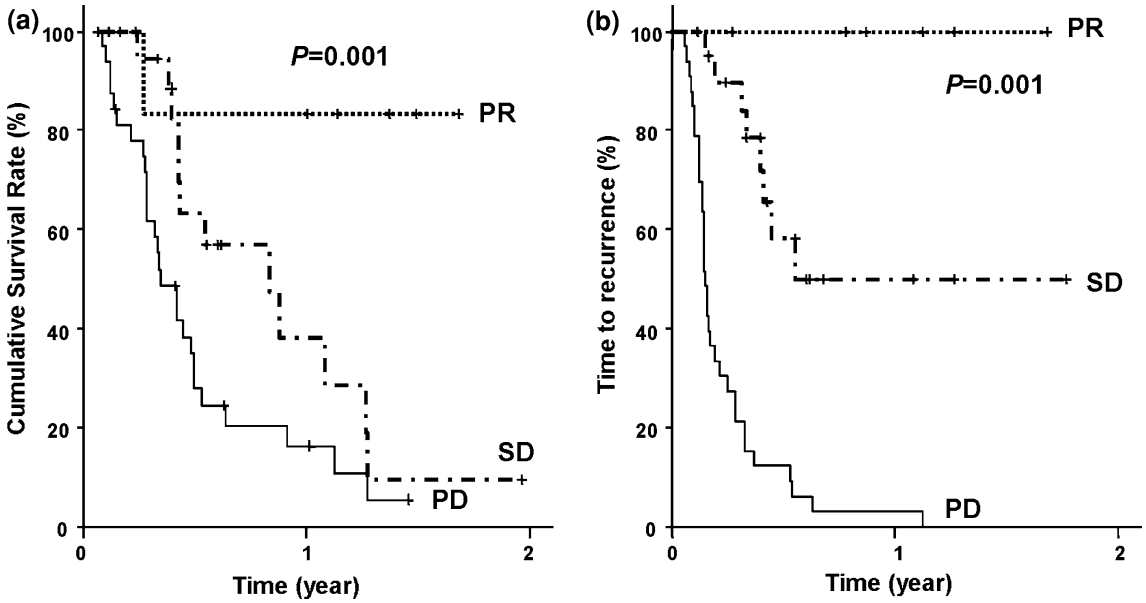


**Fig. 4** Comparison of **a** OS and **b** TTP in patients showing different response to treatment. OS and TTP were significantly longer in the partial response group compared with stable disease or progressive disease groups, and the stable disease group displayed significantly prolonged OS and TTP compared with the progressive disease group (median OS, not reached vs. 304 vs. 127 days, $P = 0.001$; median time to progression,. not reached vs. 202 vs. 54 days, $P < 0.001$). *PR* partial response, *SD* stable disease, *PD* progressive disease

**Table 4** Difference in baseline characteristics among patients with partial response, stable disease and progressive disease

| Parameter | PR ($n = 6$) | SD ($n = 21$) | PD ($n = 33$) | $P$ value† | $P$ value‡ |
|---|---|---|---|---|---|
| Age (years)* | 56 (48–64) | 54 (31–69) | 53 (30–69) | 0.508 | 0.341 |
| Male (%) | 6 (100) | 17 (81) | 29 (87.9) | 0.311 | 0.760 |
| Causes, viral (%) | 6 (100) | 17 (81) | 30 (90.9) | 0.348 | 0.492 |
| Staging | | | | | |
| CLIP 1–3 (%) | 5 (83.3) | 11 (52.4) | 12 (36.4) | 0.058 | 0.077 |
| BCLC stage B (%) | 0 (0) | 5 (23.8) | 3 (9.1) | 0.311 | 0.285 |
| Tumor size (cm) ≤15 (%) | 6 (100) | 19 (90.5) | 24 (72.7) | 0.221 | 0.048 |
| Tumor number single (%) | 2 (33.3) | 0 (0) | 3 (9.1) | 0.020 | 0.814 |
| Portal vein thrombosis (%) | 6 (100) | 16 (76.2) | 30 (90.9) | 0.311 | 0.285 |
| Previous treatment (%) | 2 (33.3) | 10 (47.6) | 11 (33.3) | 0.791 | 0.379 |
| Antiviral treatment (%) | 3 (50) | 7 (33.3) | 11 (33.3) | 0.417 | 0.765 |
| ALT (IU/L)* | 29 (22–202) | 35 (18–154) | 51 (10–641) | 0.378 | 0.128 |
| Total bilirubin (mg/dl)* | 0.9 (0.8–1.4) | 0.8 (0.3–2.3) | 0.9 (0.4–2.5) | 0.622 | 0.582 |
| PT INR* | 1.08 (1.01– 1.30) | 1.14 (0.97–1.79) | 1.13 (0.92–1.56) | 0.447 | 0.853 |
| AFP level (ng/ml)* | 51.9 (4.8–82000) | 2347 (3.1–1558000) | 2274 (2.7–159800) | 0.240 | 0.670 |

*PR* partial response, *SD* stable disease, *PD* progressive disease, *ALT* alanine aminotransferase, *PT* prothrombin time, *AFP* α-fetoprotein

* Expressed as median (range); † comparison between PR vs. SD + PD; ‡ comparison between PR + SD vs. PD

12.0 months [11]. Presently, the response rate and the overall survival were poorer overall as well as in each treatment group compared to the previous studies. This is likely because the patients recruited for the present study had a greater tumor burden as described in baseline characteristics. At the time of treatment, more than 80% patients had portal vein thrombosis and liver tumor burden >50%, and more than 90% of patients had hepatic reserve function of Child–Pugh class A. As shown in the result, tumor burden was associated with response rate and response rate was the most important factor affecting survival rate. As for the poor results in each treatment group, especially in low-dose group, the etiology of underlying liver disease could affect the response rates. In this present study, most of patients had HBV infection as the underlying cause of HCC and recent study had reported that low dose of HAIC was less

**Table 5** Treatment related toxicity

| | High dose ($n$ = 36) | Low dose ($n$ = 32) |
|---|---|---|
| Anemia Grade I | 2 | 1 |
| Neutropenia Grade I/II/III | 3/1/1 | 2/1/1 |
| Thrombocytopenia Grade I/II | 3/1 | 1/1 |
| Hyperbilirubinemia Grade I/II/III | 4/2/1 | 2/1/1 |
| Gastrointestinal toxicity Grade I/II | 6/3 | 5/2 |
| Lung abscess Grade III | 0 | 1 |
| Femoral port infection Grade I/III | 0/1 | 1/0 |
| Femoral port occlusion | 0 | 1 |

effective for advanced HCC due to HBV infection than HCC due to HCV or alcohol [18].

In this study, the doses of the chemotherapeutic regimens were randomly given and the effect was prospectively compared. A previous report suggested that high-dose HAIC might result in better tumor response and low-dose HAIC might be safer than high-dose HAIC, but the latter produces more discomfort because of the necessity to remain in bed 6–8 h daily, 5 days a week for 4 weeks [11]. For this reason, in this study, the treatment interval in low-dose group was prolonged compared to previous studies [7, 10, 12, 14] to alleviate patient's inconvenience and reduce the toxicity. As a result, the total dose of the chemotherapeutic agent in low-dose group was smaller than the dose of the previous study reporting low-dose HAIC. This reduced dose could explain the lower efficacy of low-dose HAIC of this study compared to previous studies. In the result of this study, the adverse effects such as toxicity, dose reduction and treatment delay did not differ statistically between either treatment groups. Concerning the response rate, the high-dose HAIC regimen seemed to be more effective because PR was achieved only in the high-dose group, and the objective response rate was significantly better in the high-dose group. Meanwhile, disease control rate as well as TTP and OS were slightly improved in the high-dose group, although not statistically significant. This might reflect the relatively short duration of follow-up; consistent with this speculation, most of the patients (5/6, 83.3%) achieving PR were alive at the end of follow-up. Interestingly, in the subgroup with HBV infection, the response rate of high-dose group was similar to previous report [11] and TTP and OS of high-dose group was significantly improved when compared with those of low-dose group. These results suggested that high-dose HAIC might be more effective than low-dose HAIC in patients with advanced HCC associated with HBV infection.

Overall, the tumor response rate was the only factor affecting patient survival in multivariate analysis, which is similar to previous findings [11, 12]. Patients with PR and SD showed prolonged median TTP and significantly longer OS than patients with PD. Furthermore, tumor progression could be inhibited and survival benefit could be achieved in patients who did not demonstrate definite tumor regression by either HAIC treatment. In a previous study using a high-dose regimen, tumor vascularity and AFP level were decreased in patients with SD [11]. Although these changes were not shown presently, tumor growth seemed to be controlled in the SD group. Comparison among patients with

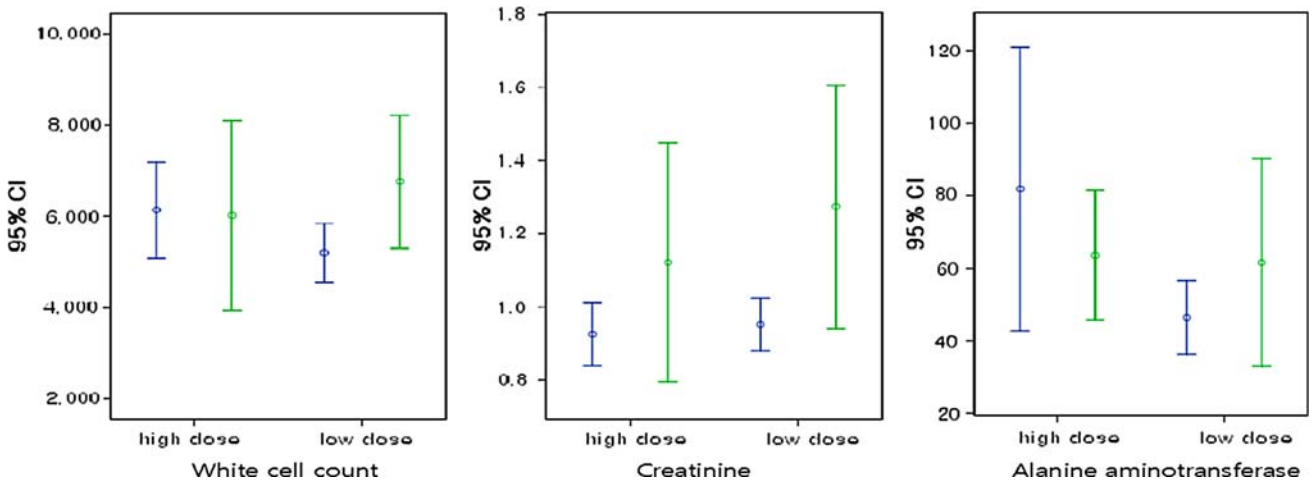


**Fig. 5** Changes in white cell count, creatinine and alanine aminotransferase level before and after high-dose and low-dose HAIC treatment. These laboratory values did not change significantly after treatment in both treatment groups. The *former bar* in each group indicated the values before the treatment and the *latter bar* indicated the values after the treatment

PR, SD, and PD showed that disease control rate (CR + PR + SD) was associated with the largest tumor size and objective tumor response (CR + PR) was associated with tumor number. This suggests that smaller tumor burden expressed by largest tumor size or tumor number is more likely controllable, although overall the tumor burden was considerable in both groups.

There are some limitations in this study. First, the number of enrolled patients was relatively small, making it more difficult to demonstrate the difference of OS and TTP between the two groups. However, it was very hard to find and enroll those who had advanced HCC staging (over TNM stage 3) with good hepatic reserve function and ECOG 0-1 during such confined duration. Second, the evaluation of quality of life was not performed formally. The 5 days of low-dose treatment duration could disturb the patient's quality of life. However, because the interval of chemotherapy was prolonged in the low-dose group compared to previous studies, the result might be comparable between the groups.

In conclusion, both HAIC regimens are tolerable and comparable in adverse effect. High-dose HAIC is more effective in tumor response but does not show a definite survival benefit compared to low-dose HAIC. Further long-term prospective and randomized studies with larger population are needed to confirm both therapeutic and survival benefit of either treatment group.

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**Conflict of interest statement** All authors in present study have nothing to disclose.

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