Journal of Cancer Therapy, 2015, 6, 1151-1161
Published Online December 2015 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2015.613125

Scientific Research Publishing

Efficacy of 5-Fluorouracil and High-Concentration Cisplatin Suspended in Lipiodol by Short-Term Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Received 24 September 2015; accepted 30 November 2015; published 3 December 2015

Abstract

Background: Since advanced hepatocellular carcinoma (HCC) is potentially fatal, and patients' quality of life (QOL) often deteriorates during their treatment, improving the prognosis and QOL of patients given chemotherapy is very important. In addition, cost-effective treatments are highly desirable when chemotherapy must be given repeatedly. The aim of this study was to evaluate the efficacy and usefulness of 5-fluorouracil (5-FU) and high-concentration cisplatin by short-term hepatic arterial infusion chemotherapy (3-day FPL) in advanced HCC patients. Methods: Thirty patients with unresectable advanced HCC were enrolled. The patients underwent hepatic arterial infusion chemotherapy via the implanted port system with 5-FU on days 1 - 3 and a fine-powder formulation of cisplatin in suspended pre-warmed lipiodol on day 2 every 4 to 10 weeks. Tumor response was assessed one month later with CT. Results: All patients had evidence of portal vein invasion (Vp2-4). Four patients achieved a complete response (CR), 8 patients achieved a partial response (PR), and 7 patients had stable disease (SD). The median progression-free survival (PFS) and overall survival (OS) were 198 days and 452 days, respectively. The OS was significantly long-

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How to cite this paper: Yata, Y., *et al.* (2015) Efficacy of 5-Fluorouracil and High-Concentration Cisplatin Suspended in Lipiodol by Short-Term Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis. *Journal of Cancer Therapy*, **6**, 1151-1161. http://dx.doi.org/10.4236/jct.2015.613125

er in the successful disease control group (CR, PR, and SD) than in the progressive disease group (*P* < 0.005). Conclusions: Three-day FPL was effective and tolerable in advanced HCC patients due to its shorter time of administration than conventional FP therapy. Therefore, repetitive 3-day FPL appears useful and contributes to improving the prognosis and QOL of patients with advanced HCC. In addition, this protocol is a cost-effective treatment.

Keywords

Advanced Hepatocellular Carcinoma (HCC), Portal Vein Tumor Thrombosis (PVTT), Hepatic Arterial Infusion Chemotherapy (HAIC), 5-FU, a Fine-Powder Formulation of Cisplatin, Quality of Life (QOL), Cost-Effective Treatment

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer (748,300 new cases in 2008) and the third most common cause of cancer death (695,900 deaths in 2008) worldwide [1] [2]. Patients with early-stage HCC may benefit from potentially curative treatments, including surgical resection and percutaneous local therapy such as radiofrequency ablation.

On the other hand, the majority of patients with advanced HCC have a poor prognosis [3] [4]. Sorafenib is effective and currently considered standard treatment for advanced HCC [5] [6]. However, some cases are resistant and uncontrollable with sorafenib treatment. Although a variety of therapeutic approaches for advanced HCC patients have been attempted, standard therapeutic protocols for them have not been established [7] [8].

It has been reported that repeated hepatic arterial infusion chemotherapy (HAIC) with various chemotherapeutic protocols by an implanted port system is a useful therapeutic modality for patients with advanced HCC [9]-[20]. However, these protocols tend to require a long duration of administration, which often results in deterioration of patients' quality of life (QOL) and a high cost. To improve patients' QOL with chemotherapy and develop cost-effective treatments for repeated chemotherapy in patients with advanced HCC with portal vein tumor thrombosis (PVTT) is highly desirable.

In this study, the usefulness of repeated HAIC with high concentrated cisplatin (CDDP) suspended in prewarmed lipiodol (Lip) and 5-fluorouracil (5-FU) by short-term hepatic arterial infusion chemotherapy (3-day FPL) was examined in advanced HCC patients with PVTT.

2. Patients and Methods

2.1. Patients

HCC and portal venous invasion were diagnosed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Before treatment, patients were evaluated physical examination, laboratory tests including albumin, aspartate transaminase (AST), alanine transaminase (ALT), platelets, serum alpha-feto-protein (AFP) and des-gamma-carboxy prothorombin (DCP). Advanced HCC patients were enrolled as below, who were not suitable for surgical resection, nonsurgical interventions such as percutaneous radiofrequency ablation (PRFA) or transcatheter arterial chemoembolization (TACE), and liver transplantation because of multiple HCCs involving both hepatic lobes and/or PVTT. The other inclusion criteria were as below: Child-Pugh class of A or B, preserved organ function (aminotransferase ≤4 times the institutional upper limit of normal and serum creatinine level ≤1.5 mg/dL), acceptable blood cell counts (neutrophil counts ≥1500/mm^3, and platelet counts ≥30,000/mm^3), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1. Previous antitumor therapy was allowed if it was performed >8 weeks before enrollment in this study.

Patients were not eligible if they had another concurrent type of malignancy, latest upper gastrointestinal bleeding, or any other underlying critical medical problem that would disturb participation in the study. Patient disease stage was made using the TNM staging system and Japan Integrated Staging (JIS) [21]. The JIS score was obtained by the summation of the tumor stage score (stage I indicates a score of 0, stage II indicates a score of 1, stage III indicates a score of 2, and stage IV indicates a score of 3) and the Child-Pugh class (Child-Pugh class A indicates a score of 0, class B indicates a score of 1, and class C indicates a score of 2).

Informed consent was obtained from each patient or responsible family member after the feasible complications of implanted port system and HAIC had been fully accounted. This study was certified by the Review Board of the Ethics Committee of Saiseikai Maebashi Hospital.

2.2. Implantation of the Port System

After injection of local anesthetic, the Seldinger technique was used to gain access to the femoral artery. Arteriography 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 the HCC and its feeding artery, the tip of the catheter was placed at the common hepatic artery or proper hepatic artery under fluoroscopic guidance. The proximal end of the catheter was connected to a drug delivery system (Terumo Clinical Supply Co., Tokyo, Japan) implanted in the lower abdomen subcutaneously. To prevent the occlusion of catheter, 10 mL (10,000 units) of a heparin aqueous solution were injected by the implanted port system every 3 weeks and after each cycle of chemotherapy. Hepatic angiography via the port system was performed with every treatment.

2.3. Treatment Schedule

After the infused port system had been implanted subcutaneously, patients were treated with HAIC via the port system. Patients underwent continuous hepatic arterial infusion of 5-FU (5-FU^{R}, Nippon Kayaku, Tokyo, Japan) at a dose of 500 mg/m^2 for 5 hours on Days 1 - 3 and a fine powder formation of cisplatin (IAcall^{R}, Nippon Kayaku, Tokyo, Japan) at a dose of 50 mg that was suspended with 5 mL of warmed Lip (10 mg/mL) as a bolus injection on Day 2 (**Figure 1**). Lip was warmed to 45˚C before suspension. IA-call has been developed as a fine powder formulation of cisplatin, and the concentration of IA-call is three times that of water soluble cisplatin. The efficacy of cisplatin is concentration-dependent, and Lip, an oily contrast medium, is selectively retained in HCCs through hepatic arterial infusion. Therefore, 50 mg of IA-call was suspended with 5 mL of warmed Lip to increase the concentration (20 times that of water soluble cisplatin) and retention of cisplatin.

All patients were given 5-HT [3] antagonists before HAIC as preventive antiemetic treatment. The treatment was repeated every 4 to 10 weeks until confirmation of disease progression, intolerable toxicity, or patient denies continuing treatment. Dosage modulation was made according to the degree of toxicity with each chemotherapeutic cycle. The following cycle of dosage was reduced by 20% in the case of grade 2 to 4 toxicity during the foregoing treatment. Therapeutic cycle was delayed until recovery from grade 3 or 4 toxicity.

2.4. Assessment of Therapeutic Efficacy

The primary endpoint was the response rate (complete response [CR] plus partial response [PR]), and the secondary endpoints were progression-free survival (PFS) and overall survival (OS). Imaging with contrast-enhanced CT was evaluated within 4 weeks before the start of therapy. During 3-day FPL treatment, a physical examination (including laboratory tests, toxicity evaluation) was performed every week in each cycle. Contrast-enhanced CT was examined repeatedly every cycle to evaluate the response of treatment. The tumoral responses were determined by contrast-enhanced CT or MRI at the end of each chemotherapeutic cycle according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [22]. PFS was calculated from the time of study entry to disease progression. OS was calculated from the time of study entry to the death or the last fol-

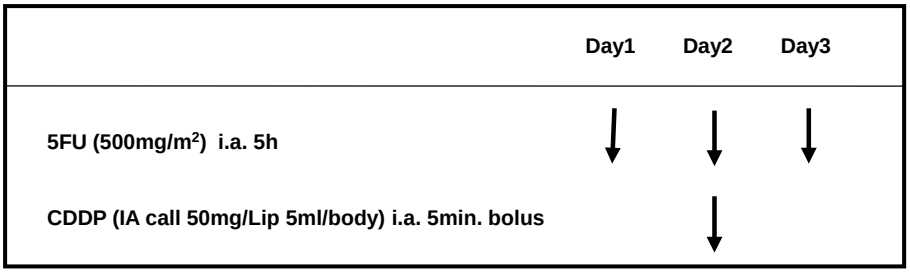

Figure 1. Treatment protocol of 3-day FPL. 5-FU is administered at a dose of 500 mg/m^2 on Days 1 - 3 and a fine powder formation of cisplatin (IA call) at a dose of 50 mg/body suspended in 5 ml of warmed lipiodol (Lip) is administered on Day 2.

low-up visit. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0).

2.5. Statistical Analysis

Baseline data are expressed as means ± standard deviation or as median and range values. Survival time was defined as the time from the date of the first treatment to the date of death or the last date of follow-up. Survival curves were calculated by the Kaplan-Meier method, and the clinical characteristics and prognostic factors were evaluated by the log-rank test. Finally, a Cox proportional hazards model was used to determine the most significant variables related to survival. A P value <0.05 was considered significant. Statistical analyses were performed using Stat View Version 5.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients' Characteristics

A total of 30 patients (19 males, 11 females; median age, 68.2 years; age range, 49 - 86 years) were enrolled between October 2007 and October 2012 in Saiseikai Maebashi hospital. The baseline characteristics of the patients are summarized in **Table 1**. The etiology of the background liver disease was hepatitis C virus (HCV) in 24 patients, hepatitis B virus (HBV) in 2 patients, alcoholism in 1 patient, nonalcoholic steatohepatitis (NASH) in 1 patient, and non HBV non HCV (NBNC) in 2 patients. All 30 patients had the portal vein invasion in Vp2-4 (the second branch to the main trunk). Twenty-eight patients (93.3%) had stage IV-A disease. Fourteen patients had ≥50% of their liver replaced by the tumor. The median serum AFP was 3527 ng/mL (4.0 - 50,000 ng/mL), and the median DCP was 671.1 mAU/ml (10.0 - 5180 mAU/mL).

Table 1. Characteristics of patient at the baseline.

	3-day FPL	Total or Range
Age (65 yrs ≤/65 yrs>)	17/13	30 (49 - 86)
Gender (male/female)	19/11	30
JIS Score (1/2/3/4)	0/2/20/8	30
Child-Pugh class (A/B)	22/8	30
Etiology, HCV/HBV/alcohol/NASH/NBNC	24/2/1/1/2	30
PS (0/1)	(16/14)	
Stage (III/IV-A)	2/28	30
Tumor type (Nodular/diffuse/massive)	7/8/15	30
Tumor size (cross-sectional area on imaging) (≥50%/<50%)	14/16	30
Hospitality stay (day: mean ± SD)	22.2 ± 16.0	(8 - 85)
PVTT (Vp2/Vp3/Vp4)	12/16/2	30
Albumin (g/dL)	3.3 ± 0.5	(42.5 - 4.3)
AFP (ng/ml)	3527.0 ± 11124.4	(4.0 - 50,000)
DCP (mAU/ml)	671.1 ± 1155.3	(10.0 - 5180)
Platelets ($\times 10^4/mm^3$)	11.8 ± 4.8	(3.2 - 24.5)
AST (IU/L)	69.5 ± 32.3	(28.0 - 134.0)
ALT (IU/L)	46.9 ± 23.0	(16.0 - 104.0)
BUN (mean ± SD)	15.9 ± 5.6	(7.7 - 32.4)
Creatinin (mean ± SD)	0.8 ± 0.2	(0.4 - 1.4)
FPL Total Course(mean ± SD)	2.5 ± 1.5	(1 - 7)

Data are number of patients or mean ± standard deviation. HCV: hepatitis C virus; HBV: hepatitis B virus; NASH: non alcoholic steatohepatitis. PVTT: portal vein tumor thrombosis; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothorombin; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

3.2. Response to Treatment

A total of 73 courses of HAIC were administered with a median of 3 courses per patient (range, 1-7 courses). Of the 30 patients, 4 (13.3%) achieved a CR, 8 (26.7%) experienced a PR, and 7 (23.3%) experienced SD, 11 patients (36.7%) experienced PD. Consequently, the response rate was 40.0%, and 19 patients (63.3%) achieved successful disease control (SDC) with this protocol.

3.3. Survival

The Kaplan-Meier analysis was used to calculate the median PFS at 198 days and the median OS at 452 days. The 1, 2, and 3-year cumulative PFS rates were 28.6%, 10.5%, and 10.5%, respectively (**Figure 2**). The 1, 2, and 5-year cumulative OS rates were 53.3%, 31.1%, and 23.3%, respectively (**Figure 3**). The OS rate was significantly longer in the DC group (CR + PR + SD) than in the PD group ($P < 0.0001$) (**Figure 4**). The one-year survival rate was 82.1% in the DC group and 36.8% in the PD group. The duration of survival demonstrated a close correlation with disease control after chemotherapy.

3.4. Prognostic Factors

The prognostic factors affecting patient survival were analyzed by evaluating the potential parameters (**Table 2** and **Table 3**). Univariate analysis showed that four significant prognostic factors were correlated with survival: age ($P = 0.05$), tumor size ($P = 0.001$), PT activity ($P = 0.05$), and therapeutic effect ($P = 0.001$) (**Table 2**). Multivariate analysis showed that therapeutic effect was the only independent prognostic factor for survival ($P = 0.01$) (**Table 3**). Univariate analysis identified three significant prognostic factors that were correlated with PFS:

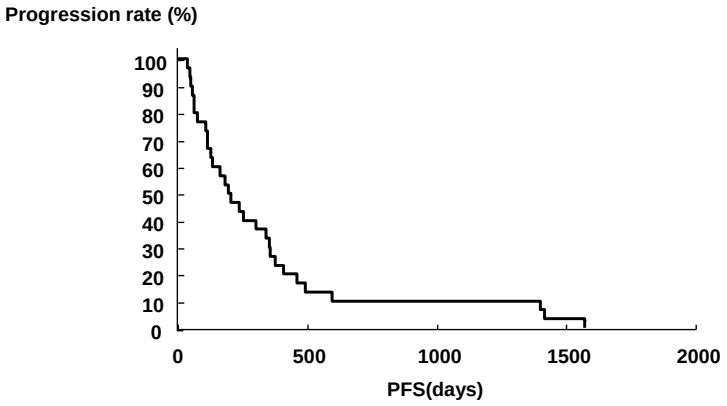

Figure 2. Progression free survival of all treated patients.

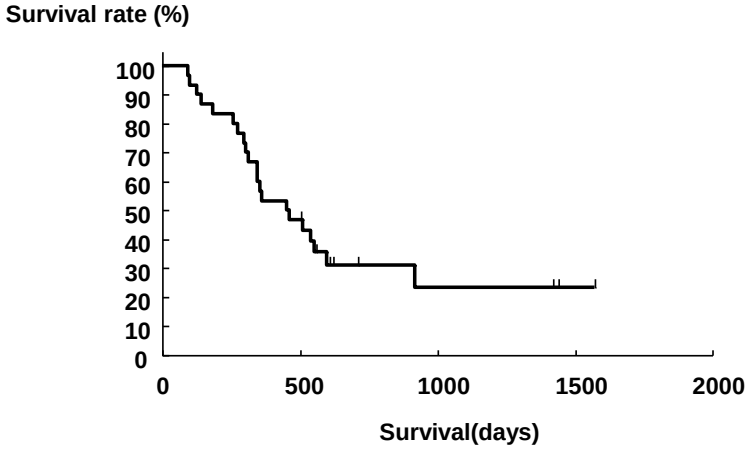

Figure 3. Overall survival of all treated patients.

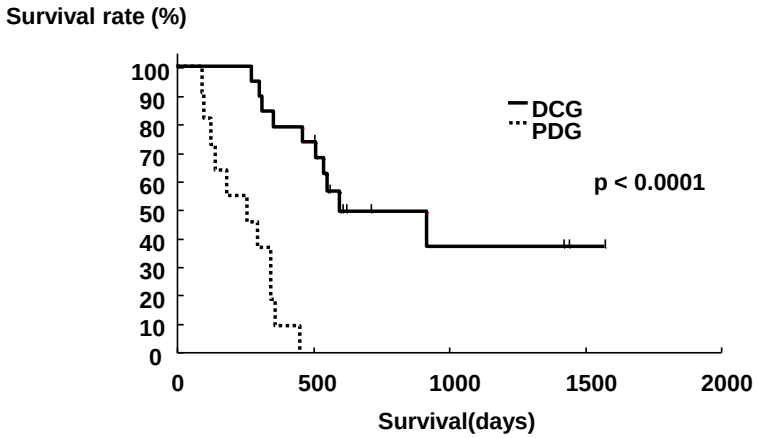

Figure 4. Comparison of the overall survival rate between successful disease control group (DCG) and progressive disease group (PDG). The solid line indicates the successful disease control group (DCG), dashed line, the progressive disease group (PDG). OS was significantly higher in the DCG (log-rank test: $P = 0.01$).

Table 2. Univariate analysis of prognostic factors for survival.

		P value
Variables		log rank test
Age	65>/65≤	0.05
CLIP Score	A/B	0.1114
JIS Score	2 & 3/4	0.1114
Therapeutic effect	Non Res/Res	0.01
Therapeutic effect	DCG/PDG	0.0001
Tumor size (cross-sectional area on imaging)	<50%/≥50%	0.01
Tumor type	Massive/Nodular	0.05
PT%	<80/≥80	0.1644
AST	<70/≥70	0.9125
ALT	<40/≥40	0.7198
AFP	<100/≥100	0.4785
DCP (mAU/ml)	<200/≥200	0.5915

Table 3. Multivariate analysis of prognostic factors for survival. Cox proportional hazard model.

Variables		Hazard ratio	95% confidence interval			*P* value
Age	<65/65≤	0.477	0.168	-	1.357	0.1652
Therapeutic effect	Res./Non Res.	1.647	0.430	-	6.303	0.4665
Therapeutic effect	DCG/PDG	0.130	0.027	-	0.638	0.0119
Tumor size (cross-sectional area on imaging)	<50%/≥50%	0.614	0.224	-	1.685	0.3437
PT%	<80/≥80	1.372	0.456	-	1.124	0.5736

tumor size (P = 0.01), PT activity (P = 0.05), and therapeutic effect (P = 0.0001) (**Table 4**). Multivariate analysis revealed that therapeutic effect was the only independent prognostic factor for PFS (P = 0.02) (**Table 5**).

3.5. Adverse Effects and Complications

The patients were assessed for toxicities and complications related to HAIC. The major toxicities and complications associated with treatment are shown in **Table 6**. The hematologic toxicities were mild except in 1 patient (3.3%) with grade 4 thrombocytopenia, although there was no bleeding. Consequently, all toxicities were tolerable and transient, and they were favorably treated with conservative therapy. The major clinical problems were one case of hepatic failure and two of gastro-intestinal ulcers induced by HAIC. However, all of these cases also recovered without any problems by conservative treatment, and the hepatic failure case achieved CR with this treatment eventually.

Table 4. Univariate analysis of prognostic factors for PFS.

Variables		*P* value log rank test
Age	65>/65≤	0.1606
CLIP Score	A/B	0.6438
JIS Score	2 & 3/4	0.6438
Therapeutic effect	Non Res/Res	0.001
Therapeutic effect	DCG/PDG	0.0001
Tumor size (cross-sectional area on imaging)	<50%/≥50%	0.05
Tumor type	Massive/Nodular	0.6332
PT%	<80/≥80	0.5664
AST	<70/≥70	0.05
ALT	<40/≥40	0.8398
AFP	<100/≥100	0.9007
DCP (mAU/ml)	<200/≥200	0.9644

Table 5. Multivariate analysis of prognostic factors for PFS. Cox proportional hazard model.

Variables		Hazard ratio	95% confidence interval			*P* value
Therapeutic effect	Non Res/Res	2.617	0.854	-	8.024	0.0923
Therapeutic effect	DCG/PDG	0.210	0.055	-	0.801	0.0223
Tumor size (cross-sectional area on imaging)	<50%/≥50%	0.753	0.305	-	1.856	0.5376
PT%	<80/≥80	0.942	0.408	-	2.176	0.8885

Table 6. Adverse effects and complications of 3-day FPL. All adverse effects were cured without severe problems.

Adverse effects (transient)

- Fever, appetite loss, chillness, nausea, vomiting (Grade 1 - 2)
- Thrombocytopenia; 1 case (Grade 4→ platelet transfusion)
- No renal dysfunction
- No neurological disorder

Complications

- Hepatic failure (CR was achieved); 1 case-recovered by treatment
- Gastro duodenal ulcer; 2 cases-recovered by treatment
  - ✧ placement to SMA; 1 case
  - ✧ anastomosis of hepatic artery and gastric artery; 1 case; aberration of CDDP
- Reactive gastric tumor (hyperplastic polyp), 1 case
- Infection around the implanted-port system, 2 cases
- Hematoma around the implanted-port system, 2 cases

The reason of hepatic failure was considered to be cisplatin or 5FU-related toxicity. However, this toxicity recovered to baseline levels within 1 month. In 3 patients, a hematoma occurred around the implanted port system. In all cases, the port systems were removed, and the patients reinitiated HAIC after the new implanted port system.

3.6. Case Presentations

One of the patients who achieved a CR had previously been treated with sorafenib (case 1, 84 yrs male). Although he was 84 yrs and his HCC had progressed despite sorafenib treatment, his HCC decreased completely with 3-day FPL treatment **(Figure 5)**. Similarly, a case of advanced HCC with inferior vena cava syndrome achieved CR (case 2, 63-yrs male); the vena cava syndrome and leg edema also decreased drastically **(Figure 6)**.

4. Discussion

The aims of the treatment of advanced HCC patients are to improve survival and maintain the QOL of patient's higher. HAIC has been reported to be valuable as a palliative treatment for advanced HCC patients [9]-[20]. By

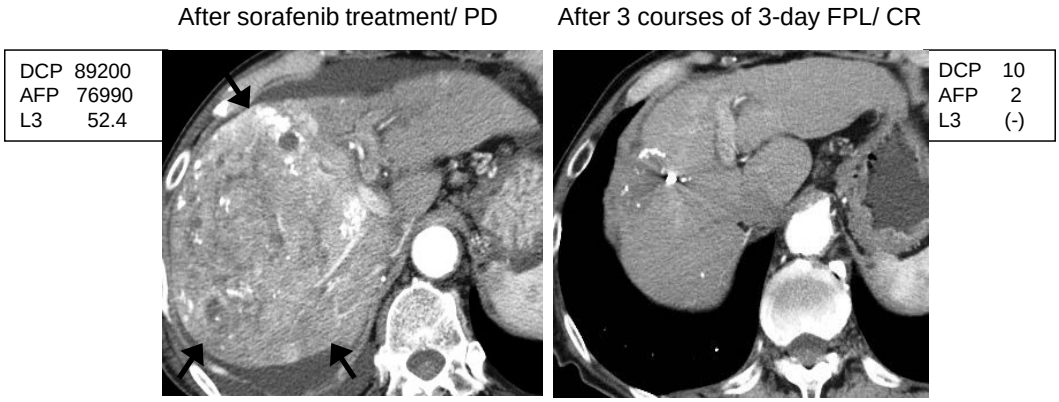

Figure 5. Abdominal CT findings before and after 3-day FPL treatment (case 1). An 84-year-old male, diffuse type HCC with liver cirrhosis related HCV. Massive diffuse type HCC was shown in right lobe (a) and sorafenib as pre-treatment have resulted in non-effective. After 3-day FPL HCC was dramatically diminished and resulted in CR (b). All tumor markers were also completely decreased.

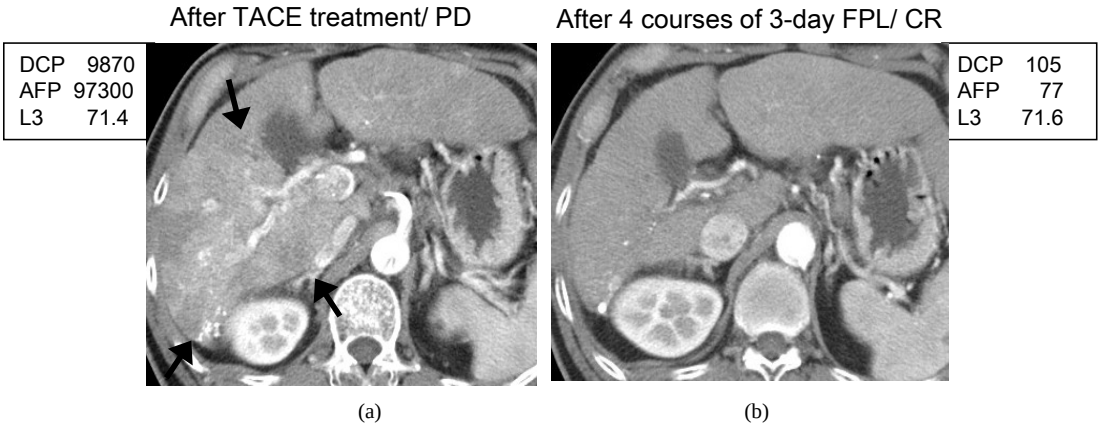

Figure 6. Abdominal CT findings before and after 3-day FPL treatment (case 2). A 63-year-old male, diffuse type HCC with liver cirrhosis related HCV. Inferior vena cava (IVC) was oppressed by diffuse type HCC before treatment (a) and TACE as pre-treatment have resulted in non-effective. After 3-day FPL, HCC and oppression of IVC were apparently diminished, and resulted in CR (b). Tumor markers except AFP-L3 were also decreased. TACE, transcatheter arterial chemoembolization.

means of HAIC, chemotherapeutic agents are delivered into the hepatic arterial branch feeders of the tumors via an implanted port and selective catheterization directly with a high local concentration at the tumor and lower toxicity than with systemic chemotherapy. In addition, usage of the implanted port could improve the patient's QOL during chemotherapy, allowing repeated, continuous administration.

Presently, sorafenib is effective and currently thought to be standard treatment for advanced HCC worldwide [5] [6] [23]. However, some cases are resistant and uncontrollable with sorafenib treatment. On the other hand, there are some advanced HCC cases in which HAIC is effective despite other treatments, including sorafenib showed no desirable effects [20]. Our case 1 also showed that 3-day FPL was dramatically effective in a sorafenib-resistant case (**Figure 5**). In this case, 3-day FPL is thought to be one of the options, and HAIC is still a useful approach for advanced HCC even in elderly patients.

The various chemotherapeutic drugs (5-FU, cisplatin, epirubicin, mitomycin-C, and doxorubicin, etc.) are administered respectively or in combination for advanced HCC, cisplatin and 5-FU are the most generally utilized drugs for HCC [11]-[19]. It has been reported that intra-arterial infusion of cisplatin with 5FU is more effective than cisplatin alone in terms of effectiveness and tolerability [15]. There have also been several reports that low-dose cisplatin and 5-FU therapy was effective in advanced HCC patients with PVTT [12]-[14]. All the more, repeated HAIC consisted of low doses cisplatin and 5-FU in advanced HCC has accomplished preferable outcomes [12] [24] [25].

It has been reported that cisplatin powder has good effects on unresectable HCC [26] [27]. The cytotoxic activity of cisplatin is concentration-dependent, and the concentration of cisplatin powder can be three times higher than that of water soluble cisplatin. The desirable strategy for chemotherapy is to utilize the most effective agents at the maximum dosages over a relatively short duration. Taking into consideration, the advanced HCC cases were treated with cisplatin powder and 5-FU in this study.

It has been reported that cisplatin with Lip suspension is more effective than cisplatin alone for advanced HCC using a drug delivery system (DDS) [28]. All the more, compared with epirubicin-Lip emulsion [29], cisplatin with Lip suspension is more effective for advanced HCC with PVTT [16] [17]. It has also been reported that warmed Lip could increase the cytotoxic activity of anti-cancer drugs [30]. Furthermore, high-dose 5FU and cisplatin therapy was more effective than low-dose 5FU and cisplatin [31]. Therefore, cisplatin powder was prepared with warmed Lip suspension (50 mg/Lip 5 mL) to amplify its cytotoxic activity instead of 35 ml saline in our regimen. Eventually, in our protocol, concentration of cisplatin powder with warmed Lip suspension has about twenty times higher (cisplatin powder has three times and Lip has seven times higher concentration) than that of water soluble cisplatin.

From the viewpoint of improvement of cancer patient's QOL, to shorten duration of chemotherapy and the length of hospitalization has been recommended [26]. Our protocol consists of 3 days administration of chemo-agents in around 7 days hospitalization, whereas the conventional protocol of low-dose cisplatin and 5-FU (LFP) is consisted of 15 days administration of chemo-agents in 28 days hospitalization [12]. In this point, our protocol is designed in shorter duration and earlier discharge.

In advanced HCC patients, improving QOL is a significant factor during repeated chemotherapy. Even if the chemotherapeutic duration is longer, it might result in deterioration of the patient's QOL. Although assessing of QOL is very hard, short time administration of chemo-agents and short hospitalization is thought to have advantages in QOL. In addition, cost-effectiveness is also important in repeated chemotherapy. To solve these problems, our regimen is also designed with only 3-day short-term treatment.

In present study, the response rate was 40.0%, the median OS was 452 days, and the median PFS was 192 days. The response rate and median OS of 3-day FPL were not inferior to those of reported regimens [12]-[14]. On multivariate analysis, successful disease control was the only independent predictor of survival. Thus, HAIC with 3-day FPL appears effective in retarding tumor progression and improving survival.

Regarding adverse effects, the major clinical problems were one case of hepatic failure and two cases of gastro-intestinal ulcers induced by HAIC. Infusions of cisplatin powder/Lip may cause severe gastroduodenal side effects, including ulcers and polyps, because of the continuous effects of anti-cancer drugs by mixing cisplatin powder with Lip. Therefore, avoiding infusion of cisplatin/Lip to the gastroduodenal artery is very important, and careful administration of cisplatin is needed to prevent severe side effects. However, all of these our cases recovered without any problems with conservative treatment and the hepatic failure case achieved CR with this treatment.

There has no agreement concerning the most valuable drugs to administer by HAIC, and their optimal condi-

tions including dose and therapeutic period. As for the usefulness of chemotherapies, to assess the sensitivity of anti-cancer drugs against individual cancer cells is very important to obtain excellent long-term survival [32]. Three-day FPL seems to advantageous regimen to discern the sensitivity and effectiveness with shorter duration.

Although multiple recurrent HCC is potentially fatal and patients' QOL tends to deteriorate, HAIC with 3-day FPL was effective and improved the patients' prognosis and maintained high QOL by the shorter duration of treatment. The results of the present study demonstrated that repeated 3-day FPL in patients with unresectable advanced HCC was effective both clinically and with a low cost.

Since the limitation of present study is the numbers of patients were small and therefore difficulty of revealing the efficacy of 3-day FPL compare with conventional regimens more objectively. The prospective study should be demonstrated in the future.

5. Conclusion

In conclusion, HAIC with 3-day FPL was effective and maintaining patients' QOL higher in advanced HCC patients. Therefore, repeated 3-day FPL is worth considering in advanced HCC patients who have a favorable PS, even though portal venous invasion is present.

Acknowledgements

Declaration of personal and funding interests: none.

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