Cancer Chemother Pharmacol (2007) 59: 9–15
DOI 10.1007/s00280-006-0239-0

ORIGINAL ARTICLE

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A combination therapy with transarterial chemo-lipiodolization and systemic chemo-infusion for large extensive hepatocellular carcinoma invading portal vein in comparison with conservative management

Received: 21 November 2005 / Accepted: 1 March 2006 / Published online: 14 April 2006

Abstract *Purpose*: Hepatocellular carcinoma (HCC) invading the portal vein is a medical challenge. We evaluated the therapeutic efficacy of a combination of transarterial and systemic chemo-infusion for large HCC with portal vein thrombosis (PVT) compared with conservative management. *Patients and methods*: This was a case-control cohort study of 103 consecutive patients with Child-Pugh class A who had a large (>10 cm) HCC with PVT. The patients were assigned to receive either combined transarterial epirubicin (50 mg/m^2) plus cisplatin (60 mg/m^2) chemo-lipiodolization and systemic 5-fluorouracil (200 mg/m^2) chemo-infusion (ECF regimen) at monthly intervals ($n=80$) or conservative management ($n=23$). *Results*: The objective tumor response (21.3 vs. 0%, $P=0.011$) and overall survival (8.7 vs. 3.5 months, $P<0.001$) were significantly better in the treatment group than in the conservative group. The prognostic factors for survival were tumor type ($P=0.007$), bilobar involvement ($P=0.001$), distant metastasis ($P=0.009$) and objective tumor response ($P<0.001$) for the treatment group. Survival benefits with the treatment were also maintained in each subgroup after stratification of these variables. *Conclusions*: This study suggests that when the hepatic function is preserved, a therapeutic strategy could be more beneficial than conservative management for such a large extensive HCC. As a therapeutic option, a combination therapy using ECF regimen may provide a significantly better tumor response and survival benefit in patients with large HCC invading the portal vein.

Keywords Hepatocellular carcinoma · Portal vein thrombosis · Chemotherapy · Combination

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Despite the recent advances in treatment, there are limited options that allow a chance of cure for this disease. Surgical resection or liver transplantation are most often used as a curative strategy, but only a small proportion of the HCC population can receive these treatments due to multifocal tumor lesions or an underlying poor hepatic function. In the past decades, HCC with portal vein thrombosis (PVT) has been a treatment challenge, because most cases are either unresectable or difficult to treat with locoregional therapy. Although transarterial chemotherapy with or without embolization is generally used as a palliative treatment for unresectable HCC [2, 5, 10], there have been few studies on the clinical value of treatment

for such a large extensive tumor invading the portal vein in comparison with no treatment. In clinical practice, most HCC patients are diagnosed at a rather advanced stage, and many cases of a large HCC (>10 cm) invading the portal vein are noted at the first presentation, raising the need for an appropriate treatment for this condition. Therefore, the real impact of the chemotherapeutic approach on tumor response or patients' survival has yet to be confirmed, particularly in this population group because there are no alternative treatment options.

The transarterial approach is the most used therapeutic strategy for treating unresectable HCC, and provided a promising objective response [3, 4, 11, 14]. Nevertheless, the survival benefits with this therapy have not yet been unequivocally proven so far. There are only a few studies favoring a transarterial treatment for unresectable HCC compared with an untreated group [14, 15], whereas other studies have reported that the beneficial outcomes are uncertain [3, 6, 10, 20]. In addition, a randomized study with systemic chemotherapy has not gained a therapeutic advantage over conservative management [9]. However, these results should be interpreted with caution considering the heterogeneity among the HCC population in terms of the tumor characteristics, etiologies of the disease, or hepatic reserve. Of the many clinical variables used, the tumor size, PVT, and underlying hepatic reserve have been established as factors affecting the final outcome either during the natural course of the disease or during treatment [1, 7, 13, 15, 17, 19]. Therefore, these confounding factors need to be adjusted in order to better assess the treatment efficacy and reduce the selection bias.

This study evaluated the impact of combination therapy with transarterial chemo-lipiodolization and systemic chemo-infusion on the clinical outcome in patients who had a large advanced HCC>10 cm and PVT in comparison with patients treated symptomatically as individuals with nonmalignant end-stage liver disease. From the analysis, there was strong evidence supporting the treatment in those patients, which included both the tumor response and patients' survival. In addition, the prognostic factors for survival were also determined.

Patients and methods

Patients

This was a case-control study aimed at evaluating the therapeutic efficacy of combination therapy with transarterial chemo-lipiodolization and systemic chemo-infusion for a large HCC with PVT in comparison with those receiving conservative management. From January 2001 to December 2004, patients newly diagnosed with unresectable HCC were eligible for enrollment if they fulfilled the following criteria: age between 20 and 80 years; tumor size >10 cm with a portal vein invasion; Eastern Co-operative Group performance status 0–2; and a Child-Pugh score ≤ 6. The patients were excluded from the study if they had one or more of the following: evidence of hepatic decompensation including ascites, gastrointestinal bleeding or hepatic encephalopathy; a Child-Pugh classification of B or C; bilirubin level >3.0 mg/dl or prolongation of prothrombin time by > 3 s; or underlying cardiac or renal diseases. A total of 567 patients were newly diagnosed with unresectable HCC at our liver unit during the study period. Among these, 103 patients meeting the above criteria were consecutively enrolled in this study after written informed consent had been obtained. The patients were allocated to receive either a combination treatment of transarterial chemo-lipiodolization and systemic chemo-infusion (treatment group, $n=80$) or conservative management (conservative group, $n=23$). The treatment allocation was made at the patients' request after a full discussion with four physicians in our medical team. A diagnosis of HCC was made either histologically or based upon an elevated serum alpha-fetoprotein (AFP) levels (>400 ng/ml) with the typical radiological findings. The presence of a portal vein invasion was determined by the computed tomography (CT) findings. The gross type of the tumor was defined according to the extent of demarcation. The well-demarcated type comprised of those tumors where more than 50% of the tumor boundary was defined. The poorly demarcated type comprised of those tumors with 50% or less of the tumor boundary defined.

Treatment methods

For the treatment group, all patients were fasted overnight before the procedure, and an intravenous hydration of 2 l of half saline with diuretics was given in order to prevent renal toxicity. The femoral artery was catheterized under fluoroscopy, and a portogram and hepatic arteriogram were then performed to show the PVT and to estimate the size, shape, and location of the tumor. Patients in the treatment group underwent a transarterial infusion of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) in a mixture of 5–10 ml of lipiodol (Guerbet, Aulnay-sous-Bois, France) without gelfoam embolization, and received an additional systemic infusion of 5-fluorouracil (5-FU) (200 mg/m^2) for 12 h (ECF regimen) after completing the transarterial procedure. Unless there was a contraindication, the combination treatment sessions were repeated at monthly intervals. The dose or treatment interval was modified whenever any treatment-related toxicity was encountered. For the conservative group, the patients were managed as in those with non-neoplastic disease, according to symptoms. Blood tests and AFP levels were monitored serially at one-to-two monthly intervals.

Adverse effect and drug modification

The adverse events were assessed for 1–2 weeks after each cycle and upon admission for the subsequent cycle. Using the NCI-CTC criteria version 2.0, grade 3 or more

toxicity were noted. During the treatment period, the dose of chemotherapeutic agents was adjusted as described in one of our reports [8].

Assessment of tumor response

The tumor response was assessed 3 months after initiating treatment using a contrast-enhanced CT scan. The two longest perpendicular diameters of the lesion on the CT scan were used to measure the tumor burden. The treatment response was determined according to the WHO criteria [16]. A complete response (CR) was defined as the radiological disappearance of the tumor. A partial response (PR) was defined as a 50% or more reduction in the tumor burden compared with the baseline measurement. Progressive disease was defined as being a 25% or more increase in the tumor burden, or newly developed nodules, and a stable disease was defined as the status of those tumors that did not meet the above three response criteria. The objective response accounted for the sum of the CR and PR.

Statistical analysis

Where appropriate, the data was analyzed using a Student's *t* test, chi-square, and Fisher's exact test. The duration of the patient's survival was calculated from the time of enrollment to the date of death. The cumulative survival rates were estimated using the Kaplan–Meier method, and the differences were analyzed using the log-rank test. In order to identify the independent factors for survival, variables that showed a significant or marginal association ($P<0.1$) on univariate analysis were subsequently included in the multivariate Cox proportional hazard model. The continuous variables were dichotomized at their median value. Using SPSS 11.5, a P value <0.05 was considered significant.

Results

Study population

Table 1 shows the baseline characteristics of all 103 patients enrolled in this study. The patients were 84 males and 19 females, aged 56.0±12.1 years, and the mean tumor size was 12.2 ± 2.8 cm. At enrollment, 36 patients (35.0%) had distant metastases; lung metastasis in 14 and 3 patients, and abdominal lymph node/adrenal metastasis in 6 and 2 patients, for the treatment group and conservative group, respectively. The other 11 patients had multiple metastases in lung, abdominal cavity, bone, or spleen. There was no difference between the two groups in terms of age, gender, cause of HCC, Child-Pugh score, AFP level, or tumor characteristics.

Tumor response and survival

For the treatment group, a total of 410 courses of the combination session were performed, with each patient receiving a median of 5 courses (range 1–20). There was no CR in either group during the study period. In the treatment group, 17 patients (21.3%) showed a PR, 29 patients (36.3%) progressed, and 34 patients (42.5%) had a stable tumor size. In the conservative group, 21 patients (91.3%) progressed, and 2 patients (8.7%) had a stable tumor size at the end of the follow-up. Therefore, the objective tumor response rate was significantly better in the treatment group than in the conservative group (21.3 vs. 0%, $P=0.011$). The estimated 6-, 12-, 18-, and 24-month survival rates were 64.4, 29.8, 17.9, and 13.4% for the combination treatment group, whereas the estimated 6- and 12-month survival rates were 29.8 and 0% for the conservative management group. The survival rate was significantly better in the treatment group than

Table 1 Baseline characteristics of all 103 patients in the two groups

	Treatment group ($n=80$)	Conservative group ($n=23$)	P value
Age (years)	55.5 ± 11.4	56.9 ± 13.1	0.611
Sex (male:female)	65:15	19:4	0.438
Causes of HCC			0.831
HBV/HCV/alcohol/others	62/7/5/6	18/1/1/3	
Child-Pugh score			0.373
5	50 (62.5%)	12 (52.2%)	
6	30 (37.5%)	11 (47.8%)	
AFP (ng/ml)	1,138.3 ± 1,025.2	905.0 ± 919.3	0.336
Tumor size (cm)	12.1 ± 2.3	12.4 ± 2.9	0.434
Tumor type			0.478
Well-demarcated	38 (47.5%)	9 (39.1%)	
Poorly demarcated	42 (52.5%)	14 (60.9%)	
Lobar involvement			0.581
Unilobar	40 (50.0%)	10 (43.5%)	
Bilobar	40 (50.0%)	13 (56.5%)	
Distant metastasis			0.606
Absent	51 (63.8%)	16 (69.6%)	
Present	29 (36.2%)	7 (30.4%)	

HCC hepatocellular carcinoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* α-fetoprotein

in the conservative group (median 8.7 vs. 3.5 months, $P<0.001$, log-rank test) (Fig. 1).

Prognostic factors for survival in the treatment group

The prognostic factors affecting the patients' survival in the treatment group were investigated by examining ten potential variables (Table 2). Univariate analysis revealed four poor prognostic factors related to survival: poorly demarcated type ($P=0.007$), bilobar involvement of the tumors ($P=0.001$), distant metastasis ($P=0.009$), and an absence of an objective response ($P<0.001$). In addition, an AFP level of > 767 ng/ml was found to be marginally associated with a poor survival ($P=0.072$). Of these, multivariate analysis identified the objective tumor response (Odds ratio [OR]=9.260; 95% confidence interval [CI] 3.268–26.236; $P=0.001$), and gross type of the tumor (OR=1.826; 95% CI 1.073–3.108; $P=0.026$) as the two independent factors for survival (Table 3).

In order to confirm the survival benefit with the combination treatment, the four prognostic factors were further stratified, and then survival was re-evaluated and compared between those receiving treatment and conservative management in each subgroup. As a result, there was a consistent survival benefit with the combination treatment using the ECF regimen in each subgroup except for those with an extrahepatic metastasis (Table 4).

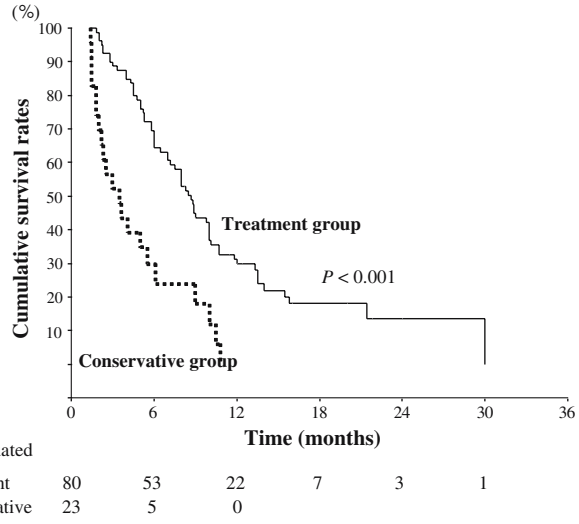

Fig. 1 Cumulative survival of the patients. The overall survival was significantly longer in the treatment group than in the conservative group (median 8.7 vs. 3.5 months, $P<0.001$, log-rank test)

Table 2 Univariate analysis of prognostic factors for survival in the combination treatment group

	Treatment group ($n=80$)	
	Median survival (months)	*P* value
Age (years)		
≤60 vs. >60	8.9 vs. 8.4	0.607
Sex (male:female)		
Male vs. female	8.0 vs. 11.8	0.297
Causes of HCC		
HBV vs. others	8.1 vs. 8.9	0.788
Child-Pugh score		
5 vs. 6	8.8 vs. 6.1	0.233
AFP (ng/ml)		
≤767 vs. >767	9.9 vs. 8.0	0.072
Tumor size (cm)		
≤15 vs. >15	8.8 vs. 8.0	0.526
Tumor type		
Well vs. Poorly demarcated	10.0 vs. 7.5	0.007
Lobar involvement		
Unilobar vs. bilobar	10.7 vs. 7.2	0.001
Distant metastasis		
Absent vs. present	9.8 vs. 7.4	0.009
Objective tumor response		
Present vs. absent	21.4 vs. 7.3	<0.001

Objective tumor response was defined as the sum of complete response and partial response
HCC hepatocellular carcimoa, *AFP* α-fetoprotein

Adverse events related to treatment

Table 5 shows the acute complications that appeared within 1 week of treatment. Overall, patients well tolerated the treatment. Most of the acute events including abdominal pain, vomiting, diarrhea, fever or ileus regressed spontaneously, or subsided with symptomatic care, and no treatment-related mortality was encountered. For patients with post-treatment neutropenia and/or hepatic events, dose reduction was made according to the protocol [8]. One patient developed jaundice and ascites after chemotherapy, leading to premature termination of the treatment. The other patients completed the procedure without any significant treatment delays attributable to acute toxicity.

Table 3 Multivariate analysis of poor prognostic factors for survival in the combination treatment group

	Treatment group ($n=80$)	
	OR (95% CI)	*P* value
AFP (ng/ml)		
>767	1.145 (0.638–2.053)	0.650
≤767	1	
Tumor type		
Poorly demarcated	1.826 (1.073–3.108)	0.026
Well-demarcated	1	
Lobar involvement		
Bilobar	1.488 (0.871–2.541)	0.146
Unilobar	1	
Distant metastasis		
Present	1.195 (0.704–2.029)	0.510
Absent	1	
Objective tumor response		
Absent	9.260 (3.268–26.236)	0.001
Present	1	

Objective tumor response was defined as the sum of complete response and partial response
AFP α-fetoprotein, *OR* odds ratio, *CI* confidence interval

Table 4 Difference in survival between the two groups after stratification of each prognostic variable

	Treatment group (months[a])	Conservative group (months[a])	*P* value
AFP (ng/ml)			
≤767	9.8	5.0	0.0024
>767	7.0	2.3	0.0001
Tumor type			
Well-demarcated	10.0	5.0	0.0017
Poorly demarcated	7.5	2.3	0.0010
Lobar involvement			
Unilobar	10.7	5.5	0.0068
Bilobar	7.2	2.3	0.0002
Distant metastasis			
Present	7.5	3.6	0.1183
Absent	9.8	2.3	<0.0001

AFP α-fetoprotein
[a] Values indicate the median

Table 5 Adverse events related to combination therapy

Adverse events	Number of patients
Abdominal pain	17 (21.3%)
Vomiting	15 (18.8%)
Fever (≥38.0°C)	11 (13.8%)
Neutropenia	6 (7.5%)
Ascites	5 (6.3%)
Diarrhea	4 (5.0%)
Pleural effusion	3 (3.8%)
Ileus	3 (3.8%)
Gastrointestinal bleeding	2 (2.5%)
Thrombocytopenia	2 (2.5%)
Arrhythmia	1 (1.3%)

Cause of deaths

Overall, 62 (77.5%) of the 80 patients in the treatment group and 21 (91.3%) of the 23 patients in the conservative group died during the follow-up. The causes of death are listed in Table 6. In both groups, the most common cause of death was tumor progression, and a minority of the patients died from a deteriorating hepatic function without any evidence of tumor progression, sepsis, and gastrointestinal bleeding. One patient in the conservative group was still alive after 6 months of follow-up when the final analysis was done. Two in the treatment group and one in the conservative group were lost to follow-up, and were treated as censored values in the analysis.

Discussion

There is little agreement regarding a common treatment strategy for patients with unresectable HCC. Despite the general application of the transarterial approach for this setting, the identification of optimal candidates for its use is an issue of continuing debate. Earlier randomized studies failed to validate its impact on survival [3, 6, 20]. However, more recently, a few studies have provided evidence of survival gains with treatment when compared with those untreated [14, 15]. These controversies are most likely related to the selection bias of patients. The different therapeutic methodologies used in each study might also serve as an additional confounding factor in assessing the treatment outcome. Of the clinical variables, the tumor size, Child-Pugh classification, AFP levels, and PVT are known to be prognostic factors in HCC patients [6, 12, 15, 17, 19]. Therefore, an understanding of whether or not the treatment itself has a real benefit would become more evident after adjusting for these variables.

Table 6 Causes of death in each group

Causes	Number of patients in each group	
	Treatment group	Conservative group
Tumor progression	41 (66.1%)	15 (71.4%)
Hepatic failure without tumor progression	8 (12.9%)	2 (9.5%)
Sepsis	4 (6.5%)	–
Gastrointestinal bleeding	4 (6.5%)	2 (9.5%)
Tumor rupture	3 (4.8%)	1 (4.8%)
Others	2 (3.2%)	1 (4.8%)

This study concentrated on very large tumors associated with PVT, in which there would be virtually no other choice but to perform an intraarterial or systemic chemotherapy. Indeed, although patients are often observed with such an extensive tumor burden in clinical practice, there is limited data on their management. Moreover, no study has explored the treatment outcome in a far advanced HCC larger than 10 cm invading the portal vein under a clinical setting. We previously reported promising results with combination chemotherapy using an ECF regimen and a percutaneous ethanol injection therapy for unresectable HCC [8]. In view of this, the present study was carried out to determine if this combination regimen is applicable to a large extensive HCC and offers a therapeutic gain.

One of the keynotes of this study is that a combination therapy of transarterial epirubicin plus cisplatin and systemic 5-FU infusion provided a clear survival benefit in patients with very large HCC invading the portal vein compared with conservative management. More importantly, a survival benefit was also consistently noted in each subgroup after stratification of those prognostic factors. In addition, considering that the patients enrolled in this study already had a poor prognosis with respect of large tumor size and the presence of PVT, the 21.3% objective response rate appears to be comparable to those observed in previous studies [5, 6, 15, 18, 21]. Therefore, this study suggests that even though the tumor status at presentation is extensive, therapeutic applications should take priority over conservative management if the underlying hepatic function is well preserved.

Several intraarterial treatments have been used to treat HCC. These include arterial embolization, chemo-embolization, chemo-lipiodolization, intraarterial chemotherapy, and intraarterial yttrium-90 injection. Of these, only chemo-embolization has been shown to improve the survival in HCC patients [14, 15]. However, it should be noted that hepatic vascular embolization can often result in more augmentation of the ischemic insult to the liver, particularly in patients with advanced disease. Indeed, we formerly found that some patients developed post-embolization hepatic failure such as encephalopathy, ascites, or severe jaundice, which were more evident in those with more advanced tumors [8]. Considering that our patients had an advanced tumor >10 cm associated with PVT, there would be a potential risk of hepatic failure after the embolization procedure. Therefore, it is our opinion that these patients would better tolerate the non-embolizing approach such as intra-arterial chemo-lipiodolization rather than embolization therapy.

With regard to toxicity, most patients tolerated the regimen and showed only mild or transient adverse events. There was only one case of a premature termination of the procedure due to treatment-related hepatotoxicity, but there was no case of treatment-related death. The frequency of adverse events with our protocol appeared to be similar or less, compared with those of other studies [5, 10, 15].

The type of chemotherapeutic agents and the treatment schedule can affect the treatment outcome. Besides a combination mode of non-embolizing intraarterial chemo-lipiodolization and systemic chemo-infusion, our regimen and technique is unique in several ways. In an attempt to avoid treatment-related adverse events, the chemotherapeutic dose was individualized and renewed each session [8], which might explain the acceptable toxicity profile in this study. In addition, a relatively shorter treatment interval was adopted (median 4.8 weeks) compared with other studies, and the treatment was undertaken at regular intervals without any limitation of the number of treatment sessions in each patient, unless contraindicated. Overall, these could be part of the reasons for the better outcome with our treatment protocol.

The results showed the objective tumor response and tumor type to be the most important prognostic factors. These are in parallel with previous studies using other chemotherapeutic regimens [10, 12, 14]. Of note, the gross type of tumor was the sole pre-treatment factor predicting a poor outcome with the combination treatment, which suggests that the chemotherapeutic approach alone may be insufficient to control a poorly demarcated infiltrating tumor. Therefore, it is necessary to seek an alternative treatment or a combination of other modalities to enhance the anti-tumor effect in patients with this type of tumor.

This study lacks randomization, and it might be argued that the clinical benefit obtained in this study was potentially biased by the patient selection. However, large randomized studies with an untreated arm may be practically unfeasible for ethical reasons. Despite the lack of subject randomization, the present case-control study recruited a large number of patients in a consecutive manner, and there was also no difference in the baseline characteristics between the treatment and control arms. In this respect, the nature of the subject characteristics should reduce the selection bias and improve the reliability of the data. In addition, this study was limited to patients with Child-Pugh classification A, since our current approach for Child B or C patients is suboptimal or conservative, because of the potential development of hepatic failure after treatment. Therefore, whether the treatment could still offer a therapeutic gain for those with decreased liver function remains an issue that requires further evaluation.

In conclusion, a combination therapy of transarterial epirubicin plus cisplatin chemo-lipiodolization and systemic 5-FU chemo-infusion offered a promising tumor response and survival benefit in patients with large advanced HCC invading the portal vein. For patients with a poorly demarcated tumor, there is a need to add or combine alternative treatment modalities with chemotherapy in order to achieve a more enhanced anti-tumor effect. This study suggests that when the hepatic function is preserved, a therapeutic strategy could be more beneficial than conservative management for such a large extensive HCC. In this regard, the present combination therapy using ECF regimen may be a feasible treatment option for patients with a large tumor invading the portal vein.

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