The safety and clinical outcome of chemoembolisation in Child-Pugh Class C patients with hepatocellular carcinoma

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Aims and objectives

Introduction

Hepatocellular carcinoma (HCC) patients with Child-Pugh class C disease are treated with supportive care according to the BCLC staging system[1], or by liver transplantation in cases of limited tumor burden[2]. Given the shortage of donors, liver transplantation cannot be performed in all patients with Child-Pugh class C disease. Although transarterial chemoembolization (TACE) has a survival benefit over conservative management[3; 4], Child-Pugh class C is one of the contraindications for TACE[5]. According to the guidelines of the Japan Society of Hepatology, subsegmental TACE can be performed as compassionate treatments in Child-Pugh class C cases when hepatic encephalopathy and intractable ascites are absent and the serum bilirubin level is less than 3 mg/dL[6].

With advancements in microcatheter technology, selective or superselective TACE has been adapted by many interventional radiologists, resulting in excellent clinical outcomes and fewer complications[7; 8]. In actual clinical practice, occasionally TACE can be considered even in patients with Child-Pugh class C according to the patient's individualized clinical situation including the tumor burden, need for local control, and availability of liver transplantation. However, to the best of our knowledge, there has been no report on the safety and clinical outcomes of TACE in patients with decreased liver function classified as Child-Pugh class C. The aim of this study is to evaluate the safety and clinical outcome of TACE in Child-Pugh class C patients with HCC.
Methods and materials

Materials and Methods

Patients

This study was approved by our institutional review board, and the requirement for informed patient consent was waived due to its retrospective study design.

From January 2003 to December 2012, 5264 HCC patients received initial TACE in our institute according to the TACE database. The inclusion criteria were as follows: (a) patients with underlying liver cirrhosis and decreased hepatic function categorized as Child-Pugh class C, (b) HCC diagnosed either by pathology or by non-invasive imaging modalities according to American Association for the Study of Liver Diseases (AASLD) practice guidelines[9], and (c) no medical history of previous TACE. The exclusion criteria were as follows: (a) previous therapy, such as percutaneous alcohol injection, radiofrequency ablation, and surgical resection; (b) patients with ruptured HCC, (c) concomitant malignant tumors in addition to HCC, and (d) an aborted TACE procedure due to a severe arterioportal shunt. Fifty-five patients (46 men and 9 women; mean age, 54 years; range, 34-77 years) with Child-Pugh class C were included in this retrospective study.

Chemoembolization

Liver transplantation was recommended as the first treatment in all patients with Child-Pugh class C disease and a limited tumor burden within Milan criteria[10]. If liver transplantation was not feasible, the treatment strategy (TACE and supportive care) was determined for each patient based on the attending physician's recommendations and the patient's choice. Patients made their choice based on the physician's advice that TACE could delay tumor progression but that it could also increase the risk of hepatic failure. Patients who feared hepatic failure received supportive care.

All the patients underwent contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) within 40 days before TACE procedure. The methods and techniques of chemoembolization at our institution are summarized as follows: First, arteriography of the celiac and superior mesenteric arteries was performed with a 5-F angiographic catheter to evaluate the anatomical variation of the hepatic arteries, the location and extent of HCC and the tumor-feeding arteries. Superselective TACE was initially considered and performed in all technically feasible cases to minimize procedure-related complications such as hepatic function deterioration. After advancing the microcatheter with a 2.0-F tip or a 2.4-F tip into the most distal branches of tumor-feeding artery which can be technically accessible, an emulsion of iodized oil mixed with
doxorubicin hydrochloride was infused via the microcatheter until a decrease in the blood flow to the tumor was observed (Fig. 1). Additional embolization was performed with 1 mm sized absorbable gelatin sponge particles to maximize the therapeutic effect of TACE. Follow-up contrast-enhanced CT or MRI examinations were performed at intervals of 2-3-months thereafter.

**Baseline data collection**

The patients’ medical records were reviewed and the following clinical information and laboratory parameters before TACE procedure were obtained: age, sex; etiology of HCC; Eastern Cooperative Oncology Group (ECOG) performance status; Child-Pugh score; Model For End-Stage Liver Disease (MELD) score; and laboratory data, including albumin, bilirubin, the international normalized ratio (INR), creatinine, alpha-fetoprotein (AFP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). All the baseline laboratory parameters were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[11].

The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging, Okuda staging, and Cancer of the Liver Italian Program (CLIP) score of the patients were also determined from the clinical and laboratory data and an analysis of the pre-procedural contrast-enhanced CT or MRI. In addition, authors determined whether the tumor burden of the patients was within Milan criteria.

**Safety**

All adverse events and mortalities occurred within one month the after the chemoembolization were recorded. Abnormal laboratory test results after the chemoembolization were recorded and graded according to CTCAE. As laboratory test results are commonly abnormal in Child-Pugh class C patients, the severity of TACE-related adverse effects on laboratory parameters was evaluated by comparing the CTCAE grade of the laboratory abnormalities after TACE with those at baseline.

To evaluate and determine risk factors for TACE-related complications, demographic data, including age and sex, performance status, Child-Pugh score, tumor staging (AJCC/UICC staging, Okuda staging, CLIP score and MELD score), presence of PVT and laboratory parameters (albumin, bilirubin, and the INR) of the patients who developed complications or major complications were compared to those of the rest.

In addition, the duration of hospitalization of all the patients after chemoembolization was recorded.

**Treatment response**
In patients who underwent follow-up contrast-enhanced CT or MRI after TACE, two authors evaluated the tumor response to TACE and reached a consensus using modified Response Evaluation Criteria In Solid Tumors (modified RECIST)[12].

**Survival**

Survival analysis was performed, and survival curves were calculated from the time of the TACE procedure in all the patients. The follow-up of the patient ended when any of the following criteria was met: (a) death of the patient, (b) liver transplantation, or (c) the end of the study, which was 31 August 2014. If a patient underwent transplantation, the follow-up data were censored on the date of the operation.

**Statistical analysis**

Differences between the patients who developed major complications and those who did not were evaluated by Fisher’s exact test, a Student’s t test, or a Mann-Whitney U test. In addition, variables of the patients who developed major or minor complications were compared to those without any adverse events using identical statistical methods. The overall median survival times and survival curves were calculated with the Kaplan-Meier method, and subgroup comparisons were performed using a log-rank test. In addition, a Cox proportional hazards model was used for multivariate analysis. A $P$-value less than 0.05 was considered statistically significant in all the analyses.
**Fig. 1:** A 52-year-old woman with Child-Pugh class C liver cirrhosis. (a) An axial CT image obtained at arterial phase shows a 4.5cm sized arterial enhancing mass (arrowheads) in the segment 4 of the liver. Note the cirrhotic liver and large amount of ascites. (b) Celiac arteriography shows hypervascular tumor staining (arrowhead) which is supplied by two prominent feeding arteries from the left hepatic artery. (c) The tip of microcatheter (arrowhead) was placed at distal portion of one of the tumor feeding arteries which was followed by an infusion of iodized oil emulsion. (d) Thereafter, the other tumor feeding branch from left hepatic artery was selected and catheterized with a microcatheter (arrowhead), and chemoembolization was performed. Spot image obtained during chemoembolization shows additional dense accumulation of iodized oil in the tumor and oily portogram around the tumor. (e) Arterial phase image of the follow up liver CT scan shows dense accumulation of iodized oil in the previously noted HCC in the segment 4 (arrowheads) without evidence of viable tumor.

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Results

Morbidity and mortality

Mortality at 30 days was 5.5% (3/55), which included two deaths from acute hepatic failure and one from disease progression. Of these three patients, two expired in the hospital.

Major complications were observed in five (9.1%) patients. Two of these developed hepatic failure and expired, one patient developed hepatic encephalopathy, and two patients had a CTCAE grade 3 increase in AST/ALT abnormalities. In addition, two (3.6%) patients experienced puncture site bleeding or a hematoma, which required extrinsic compression. One of these also showed a CTCAE grade 1 increase in AST/ALT levels. Twenty-six (47.3%) patients showed only a CTCAE grade 1 or 2 increase in laboratory test parameters, and there were no complications in the remaining 22 (40.0%) patients.

All the patients (5/5) who developed major complications after TACE exceeded Milan criteria, whereas only 40.0% (20/50) of those without complications or with minor complications exceeded these criteria ($P = 0.015$). In addition, the patients with major complications had significantly higher T-staging ($P = 0.031$) and a higher CLIP score ($P = 0.007$) compared to those without complications or with minor complications. However, the characteristics of the patients who developed major or minor complications were not significantly different from those of the patients who had no adverse events.

Duration of hospitalization

The mean days of hospitalization was 6.3, and the median value was 3 days. Eighteen (32.7%) patients were discharged on the day after TACE without complications.

Tumor response

For 43 patients who had available follow-up contrast-enhanced CT or MRI, 19 (44.2%) showed complete responses to the TACE, 10 (23.3%) showed partial responses, 9 (20.1%) remained stable, and 5 (11.6%) progressed. The tumor responses of the patients who met Milan criteria were significantly higher ($P = 0.014$) than those of the patients who did not. Complete responses were achieved in 57.1% (16/28) of patients where the tumor burden was within Milan criteria.

Survival
At the end of the study, which was 31 August 2014, 22% (11/55) of all patients were alive. The overall median survival of all the patients after TACE was 7.1 ± 1.4 months. The results of the univariate analysis showed that the following baseline characteristics were associated with significantly higher survival rates: ECOG performance status of 1 or less, AJCC T stage 1, CLIP score of 3 or less, tumor burden within Milan criteria, absence of PVT, and low serum AFP (# 400 ng/mL) and AST (# 80 IU/L) levels. In addition, the multivariate analysis identified four independent predictive factors for a shorter survival time: ECOG performance status > 1, tumor burden exceeding Milan criteria, serum AFP > 400 ng/mL, and serum AST > 80 IU/L.
**Fig. 2**: Survival curves of the patients whose ECOG performance status 1 vs. more than 1 (median survival time, 12.9 months, 95% CI, 4.3 - 21.5 vs. 4.0 months, 95% CI, 0 - 8.2, P = 0.003).

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Fig. 3: Survival curves of the patients whose tumor burden within Milan criteria vs. beyond Milan criteria (median survival time, 10.6 months, 95% CI, 6.2 - 15.0 vs. 3.3 months, 95% CI, 2.5 - 4.1, P < 0.001).

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Fig. 4: Survival curves of the patients with serum alpha-fetoprotein (AFP) level ≤400 ng/mL vs. >400 ng/mL (median survival time, 9.1 months, 95% CI, 5.9 - 12.3 vs. 3.4 months, 95% CI, 3.2 - 3.6, P = 0.018).

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**Fig. 5:** Survival curves of the patients with serum aspartate aminotransferase (AST) level ≤80 IU/L vs. >80 IU/L (median survival time, 9.8 months, 95% CI, 6.8 - 12.9 vs. 3.4 months, 95% CI, 2.4 - 4.4, P = 0.004).

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Conclusion

Discussion

In this study, the overall incidence of TACE-related major complications in Child-Pugh class C patients was 9.1%, which is within the acceptable threshold (15%) suggested by the Quality Improvement Guidelines for Transhepatic Arterial Chemoembolization, Embolization, and Chemotherapeutic Infusion for Hepatic Malignancy of the Society of Interventional Radiology[13].

The results of our study also showed that the patients with major complications were more likely to be those whose tumor burden exceeded Milan criteria ($P = 0.015$) and who had a significantly higher CLIP score ($P = 0.003$) compared with those without complications or with minor complications. Consequently, the tumor burden of each patient seems to be closely related to the development of major complications after TACE.

In conclusion, even in patients with decreased liver function classified as Child-Pugh class C, TACE can be performed safely with the superselective technique in selected cases with a small tumor burden.

Our study has several limitations. First, as this was a retrospective study with a relatively small number of patients, there may have been a selection bias. Second, the intervals between the TACE procedure and follow-up laboratory tests, as well as the imaging studies, could not be controlled uniformly due to its retrospective nature. Third, this study did not have a matched control group, and we compared and discussed the results of our study with those of the previous literature. Therefore, further matched randomized studies with a large study population will be required to confirm our results and speculations.
References

Reference

http://evs.nci.nih.gov/ftp1/CTCAE/