Multivariate Analysis of the Predictors of Survival for Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization: Focusing on Superselective Chemoembolization

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Objective: While the prognostic factors of survival for patients with hepatocellular carcinoma (HCC) who underwent transarterial chemoembolization (TACE) are well known, the clinical significance of performing selective TACE for HCC patients has not been clearly documented. We tried to analyze the potential factors of disease-free survival for these patients, including the performance of selective TACE.

Materials and Methods: A total of 151 patients with HCC who underwent TACE were retrospectively analyzed for their disease-free survival (a median follow-up of 23 months, range: 1-88 months). Univariate and multivariate analyses were performed for 20 potential factors by using the Cox proportional hazard model, including 19 baseline factors and one procedure-related factor (conventional versus selective TACE). The parameters that proved to be significant on the univariate analysis were subsequently tested with the multivariate model.

Results: Conventional or selective TACE was performed for 40 and 111 patients, respectively. Univariate and multivariate analyses revealed that tumor multiplicity, venous tumor thrombosis and selective TACE were the only three independent significant prognostic factors of disease-free survival (p = 0.002, 0.015 and 0.019, respectively).

Conclusion: In our study, selective TACE was a favorable prognostic factor for the disease-free survival of patients with HCC who underwent TACE.
patients with HCC who underwent TACE, while we focused on the role of selective TACE.

MATERIALS AND METHODS

Patients Selection

The requirements for patients to enter the study were as follows: (a) adult patients with hepatic cirrhosis and HCC (b) a prothrombin time ratio (i.e., the normal time divided by the patient’s time) greater than 40%, (c) a platelet count higher than 40,000 per cubic millimeter (40 × 10⁹/L), (d) newly diagnosed patients with no previous treatment for the HCC, (e) the patient was ineligible for surgical resection or transplantation, (f) the patient agreed to undergo TACE.

From August 1, 1998 to July 15, 2006, a total of 151 consecutive patients with HCC who underwent TACE in our hospital met the inclusion criteria, and the medical records of the patients were retrospectively reviewed. All of the 151 patients were monitored from the time of diagnosis to the date of death or to the time of study closure, if they were still alive. The study was censored on July 15, 2007. All of the patients had a known 1-year or longer survival status. The median follow-up period was 23 months (range: 1–88 months). All but seven patients were male. Their age ranged from 44 to 82 years (mean ± SD [standard deviation]: 64.2 ± 8.5 years). The other characteristics are shown in Table 1. The Institutional Review Board (IRB) of our hospital approved this study.

The diagnosis of HCC was verified histologically by performing a percutaneous needle biopsy for 12 patients (7.9%). For the other patients, a diagnosis was established based on the characteristic radiological features on at least two imaging examinations. These examinations included ultrasound, contrast-enhanced dynamic computed tomography (CT), magnetic resonance imaging (MRI) and hepatic angiography (for the hypervascular tumors seen on two or more imaging modalities), or the use of a single imaging technique with positive findings for HCC and an associated serum α-fetoprotein level > 400 ng/mL (25). In the majority of patients, the etiology of the cirrhosis was chronic viral hepatitis B or hepatitis C (Table 1).

Chemoembolization Techniques

All patients had enhanced dynamic CT performed within four weeks prior to TACE. Informed consent was obtained for all of the patients before the procedure. All of the TACE procedures were performed by two interventional radiologists with ten and six years of experience, respectively. Hepatic angiography was performed using 5 Fr angiographic catheters, followed by superselection of arterial feeders using a microcatheter (mainly Progreat®; Terumo; Tokyo, Japan).

We administered an iodized oil-doxorubicin hydrochloride (Adriamycin; Kyowa Hakko Kogyo, Tokyo, Japan) emulsion into the feeders. The volume of the iodized oil ranged from 3 to 10 ml, and the amount of doxorubicin ranged from 20 to 70 mg. Once the flow became sluggish, gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI) that were mixed with mitomycin-C (Kyowa Hakko Kogyo, Tokyo, Japan) and the contrast material were additionally administered into the feeders.

For selective TACE, chemoembolization was performed selectively as possible in the distal arteries that fed the

| Characteristics | No. | %   |
|-----------------|-----|-----|
| Age             |     |     |
| < 66 years      | 70  | 46.4%|
| ≥ 66 years      | 81  | 53.6%|
| Underlying causes |     |     |
| Hepatitis B    | 73  | 48.3%|
| Hepatitis C    | 44  | 29.1%|
| Hepatitis B and C | 2  | 1.3%|
| Others          | 32  | 21.2%|
| Performance score |     |     |
| 0               | 89  | 58.9%|
| 1–2             | 62  | 41.1%|
| Platelet count (×10⁹/L) |     |     |
| ≥ 100,000       | 81  | 53.6%|
| < 100,000       | 70  | 46.4%|
| Portal hypertension |     |     |
| No              | 84  | 55.6%|
| Yes             | 67  | 44.4%|
| Presence of ascites |     |     |
| No              | 122 | 80.8%|
| Yes             | 29  | 19.2%|
| Child-Pugh class |     |     |
| A               | 109 | 72.2%|
| B               | 39  | 25.8%|
| C               | 3   | 2.0%|
| Serum α-fetoprotein level |     |     |
| ≤ 50 ng/mL      | 75  | 49.7%|
| > 50 ng/mL      | 76  | 50.3%|
| Tumor number    |     |     |
| Single          | 77  | 51.0%|
| 2–3             | 56  | 37.1%|
| ≥ 4             | 18  | 11.9%|
| Tumor maximal diameter |     |     |
| ≤ 3 cm          | 78  | 51.7%|
| 3–5 cm          | 44  | 29.1%|
| > 5 cm          | 29  | 19.2%|
| Tumor distribution |     |     |
| Unilobar        | 118 | 78.8%|
| Bilobar         | 33  | 21.6%|
| Portal or hepatic vein thrombosis |     |     |
| No              | 138 | 91.4%|
| Yes             | 13  | 8.6%|
| AJCC TNM staging |     |     |
| I               | 69  | 45.7%|
| II              | 56  | 37.1%|
| III / IV        | 26  | 17.2%|
tumor (24). While performing selective TACE, attempts were made to completely occlude the arterial feeders. A small amount of saline solution was then injected slowly to confirm the complete occlusion of the segmental or subsegmental arterial feeder. If the retained contrast media was partially washed out after the saline injection, then additional gelatin sponge particles were infused until complete stasis of flow was achieved.

Conventional TACE was defined as TACE at the level of the right or left lobar hepatic artery or the proper hepatic artery. When catheterization of a segmental tumor feeder failed, then TACE was performed through the right or left hepatic arteries. Conventional TACE was performed more frequently when the tumors were supplied by multiple segmental arterial feeders.

For bilobar disease, we tried to treat all the tumors by selective TACE, if possible. If the patient’s liver function was as poor as Child-Pugh class B or C, then only the larger tumors were selectively treated to preserve the liver function. When performing conventional TACE, occlusion of the arterial feeders was not intended, and only stasis of flow was obtained at the end of the procedure. This was done to minimize possible damage to the liver parenchyma.

Imaging Interpretation and Follow-up

The CT examinations were performed with an 8-slice multidetector CT scanner (Lightspeed; GE Medical Systems, Milwaukee, WI) with 5-mm collimation and 17.5 mm/sec table speed, or with a single-detector helical scanner (Prospeed Advantage; GE Medical Systems, Milwaukee, WI) with 10-mm collimation and a 10-mm/sec table speed. All the patients underwent both non-enhanced and contrast-enhanced three-phase helical CT one-month after their TACE. Two radiologists with twelve and seven years of experience, respectively, interpreted the CT and angiographic images independently, and the final decisions were reached by consensus.

A residual viable tumor was judged to be present when an enhanced portion was seen within or around the original tumor on a one-month follow-up CT scan. If no definite evidence of residual tumor was noted on this one-month follow-up CT, then 3-phase contrast-enhanced CT was performed at a 3- or 4-month interval thereafter. Local tumor progression was judged to be present when eccentric focal disappearance of the iodized oil from the lesion was seen, or an enhanced portion was seen within or at the margin of the original mass on the next follow-up CT scans after the first one-month follow-up CT scan (26, 27). Radiofrequency ablation was first considered for the recurred small tumor that was ≤ 3 cm in the maximal diameter, if the tumor was not located in a difficult location. Additional TACE procedures were performed for other tumors. Repeated procedures were based on the tumor response and the patient’s tolerance, and were not performed at a fixed time interval.

Analysis of the Prognostic Factors for Disease-Free Survival and the Image Interpretation

Disease-free survival was calculated by considering any death or recurrence as an event (28). All the patients were followed up with a standard protocol of surveillance that included performing a contrast-enhanced dynamic CT scan at one month after TACE, followed by a liver function test, a test for the serum \( \alpha \)-fetoprotein level, a dynamic CT scan and chest radiography every three months or when the serum \( \alpha \)-fetoprotein level was significantly increased (29). When recurrence was indicated by any of these examinations, the patients underwent hepatic angiography.

The disease-free survival was the only end point of this study, and this was analyzed for 20 potential prognostic factors, including 14 baseline patient factors (the patient’s age and gender, hepatitis B infection, hepatitis C infection, the presence of ascites, the serum aspartate aminotransferase [AST] level, the serum alanine aminotransferase [ALT] level, the serum albumin level, the total bilirubin level, the platelet count, the prothrombin time [INR ratio], the Child-Pugh class, the presence of portal hypertension and the performance status score), five baseline tumor factors (the serum \( \alpha \)-fetoprotein level, the tumor location that was either unilobar or bilobar, multiplicity of the tumors, the maximal tumor diameter and portal or hepatic vein tumor thrombosis), and finally one procedure-related factor (conventional versus selective chemoembolization).

Portal hypertension was defined by the presence of either esophageal varices or splenomegaly with a platelet count < 100,000/ml (30). The performance status assessment followed the guidelines of the Eastern Cooperative Oncology Group (ECOG) (31). The number of tumors was determined from the pre-embolization CT. Tumor size was determined as the maximal diameter of the nodule that was measured on the pre-embolization CT. Vascular invasion was assessed by dynamic CT and hepatic angiography. Lymph node invasion and distant metastases were assessed via a routine screening study such as ultrasonography, dynamic CT and chest X-ray. Bone scintigraphy or a brain CT was performed if suggestive symptoms were present. Abdominal lymph nodes with the shortest diameter being 10 mm or greater were regarded as metastatic nodes.
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Statistical Analysis
For the 20 potential prognostic factors of disease-free survival, univariate and multivariate analyses were performed by using the Cox proportional hazard regression model, respectively. The main focus of analysis was on the role of selective TACE. The parameters that proved to be significant on the univariate analysis were subsequently tested with the multivariate model. The backward stepwise selection (likelihood ratio) technique was used for the multivariate test. For the survival analysis, multivariate analysis was performed twice, with and without inclusion of the procedure-related factors. If any independently significant baseline prognostic factor was not dropped by the addition of a procedure-related factor, then the confounding between the baseline and procedure-related factors was regarded as insignificant. The existence of variance inflation was also checked. For continuous variables, the cut-off was set at the median giving consideration to the clinical context.

Values on the univariate and multivariate analyses, while P-values less than 0.05 were considered statistically significant. The SPSS software package (version 10.0; SPSS Inc., Chicago, IL) was used for the statistical analysis.

RESULTS
Among the 20 potential prognostic factors affecting disease-free survival, univariate analysis revealed that the presence of ascites, a higher serum α-fetoprotein level (>40 ng/mL), a bilobar tumor distribution, tumor multiplicity, the tumor size and venous tumor thrombosis were the only significant baseline prognostic factors (p = 0.046, 0.016, 0.006, 0.000, 0.022 and 0.001, respectively). In addition, selective TACE was a significant procedure-related factor on the univariate analysis (p = 0.000) (Table 2).

Multivariate analysis for the prognostic factors that affected disease-free survival on the univariate analysis revealed that tumor multiplicity, venous tumor thrombosis and selective chemoembolization were the only three independently significant prognostic factors of disease-free survival (p = 0.002, 0.015 and 0.019, respectively) (Table 3). The two independently significant baseline factors were the same irrespective of including selective TACE in the multivariate analysis, except for minute numerical changes. The variance inflation was also minimal for the three significant factors after the addition of selective TACE in the multivariate analysis.

Conventional or superselective TACE was performed in 40 and 111 patients, respectively. Superselective TACE could not be performed because of the tumor extent (28 patients) or the vascular anatomy (12 patients). Among the 40 patients who underwent conventional TACE, the 1-, 2-, 3-, 4- and 5-year overall survival rates were 79%, 50%,

Table 2. Univariate Analysis of Prognostic Factors Affecting Disease-Free Survival of Patients with Hepatocellular Carcinoma who Underwent Transarterial Chemoembolization

| Factor                              | Regression Coefficient | Standard Error | Odds Ratio (95% CI) | P value |
|-------------------------------------|------------------------|---------------|---------------------|---------|
| Age (<66 vs. ≥66 years)             | 0.187                  | 0.172         | 1.205 (0.860-1.690) | 0.279   |
| Gender (female/male)                | 0.176                  | 0.457         | 1.192 (0.486-2.922) | 0.701   |
| Performance status score (0/1-2)    | 0.347                  | 0.179         | 1.415 (0.996-2.010) | 0.052   |
| Hepatitis B infection (no/yes)      | 0.052                  | 0.173         | 1.053 (0.751-1.477) | 0.763   |
| Hepatitis C infection (no/yes)      | -0.139                 | 0.194         | 0.870 (0.596-1.271) | 0.472   |
| Serum AST level (≤40 vs. >40 units/L)| 0.223                  | 0.178         | 1.250 (0.882-1.771) | 0.210   |
| Serum ALT level (≤40 vs. >40 units/L)| 0.076                  | 0.173         | 1.079 (0.769-1.513) | 0.661   |
| Presence of ascites                 | 0.373                  | 0.187         | 1.453 (1.005-2.097) | 0.046*  |
| Serum albumin level (≥3.5 vs. <3.5 g/dL) | 0.325                  | 0.178         | 1.384 (0.976-1.962) | 0.068   |
| Total bilirubin (≥1.0 vs. >1.0 mg/dL)   | 0.063                  | 0.174         | 1.065 (0.757-1.500) | 0.717   |
| Platelet count (≥100 vs. <100 [×10^9/L]) | -0.043                 | 0.173         | 0.958 (0.682-1.344) | 0.803   |
| Portal hypertension (no/yes)        | 0.310                  | 0.176         | 1.363 (0.966-1.925) | 0.078   |
| Prothrombin time ratio (INR ≤1.15 vs. >1.15) | -0.031                 | 0.175         | 0.970 (0.688-1.366) | 0.861   |
| Child-Pugh class (A/B/C)            | 0.267                  | 0.175         | 1.306 (0.926-1.842) | 0.128   |
| Serum α-fetoprotein level (≤40 vs. >40 ng/mL) | 0.421                  | 0.174         | 1.523 (1.083-2.142) | 0.016*  |
| Tumor location (unilobar/bilobar)   | 0.574                  | 0.209         | 1.775 (1.177-2.675) | 0.006*  |
| Tumor multiplicity (single/multiple)| 0.686                  | 0.179         | 1.985 (1.397-2.820) | 0.000*  |
| Tumor size (≤3 cm vs. >3 cm)        | 0.398                  | 0.174         | 1.488 (1.059-2.093) | 0.022*  |
| Venous tumor invasion (no/yes)      | 1.104                  | 0.312         | 3.016 (1.637-5.555) | 0.000*  |
| Selective chemoembolization (no/yes)| -0.698                 | 0.197         | 0.498 (0.338-0.732) | 0.000*  |

Note.—* statistically significant (p value < 0.05); CI = confidence interval
36%, 28% and 21%, respectively. The median survival was 24 months. The number of TACE sessions ranged from 1 to 12 (average: 2.3 sessions). The 1-, 2- and 3-year disease-free survival rates were 24%, 9% and 3%, respectively. The 1-, 2- and 3-year disease-free survival rates for patients who underwent selective TACE were 30%, 12% and 4%, respectively (the median disease-free survival: 6 months). The 1-, 2- and 3-year disease-free survival rates for patients who underwent conventional TACE were 8%, 3% and 0%, respectively (the median disease-free survival: 2 months).

The initial one-month follow-up CT revealed complete loss of contrast enhancement of the tumors in 98 patients (65%). Local tumor progression occurred in 87 patients. New foci of tumor occurred in 73 patients. For the residual or recurred HCC tumors, we performed additional TACE for 60 patients, local ablative therapies for six patients and combined therapy of TACE and ablative therapies for 11 patients. Conservative management was done for the other patients. At the end of the study, 110 patients had expired. Among them, 72 patients died with recurrent HCC. There was no procedure-related mortality.

DISCUSSION

The survival benefit of TACE over conservative management has been analyzed in many previous randomized studies and review articles (8-14). However, to the best of our knowledge, there have been no randomized trials or controlled studies for determining the survival benefit of selective TACE over conventional TACE. While considering the additional cost and procedural time of segmental or subsegmental TACE, it would be necessary to evaluate whether selective TACE can induce an additional overall or disease-free survival benefit so as to compensate for the additional cost and time of performing this procedure.

We think that improved disease-free survival status can be expected by the potential merits of selective TACE as follows: (1) damage to the liver parenchyma can be restricted to the specific liver segments, and (2) the tumoricidal effect can be potentiated because the chemoembolic agents are focused into specific liver segments (21, 22). Despite these potential merits, it was not clear whether selective TACE could enhance the disease-free survival status of patients, when compared to conventional TACE. The beneficial effect of initial selective TACE might have been weakened by the high rate of intra-hepatic tumor recurrence, especially for patients with viral hepatitis-originated HCC (32). However, this study showed that selective TACE could improve the disease-free survival status of patients with inoperable HCC.

In this study, the significant baseline prognostic factors for disease-free survival were similar to the factors for tumor recurrence, as were determined by the previous studies on TACE (19, 20, 22). Further more in our study, the most powerful adverse prognostic factor of survival was portal or hepatic venous thrombosis, and similar results were found by previous studies on patients who were treated with liver resection or transplantation (33-35).

The limitations of this study are as follows. First, this was a retrospective analysis and not a randomized controlled trial. However, we did not perform a randomized controlled study between selective and conventional TACE because of the anticipated potential advantages of selective TACE. Although we did not perform a controlled study, the impact of selective TACE on patient survival was adjusted by the multivariate analysis. Second, the number of patients who underwent conventional TACE was relatively small when compared to those patients who underwent selective TACE. Third, the intrahepatic or extrahepatic tumor recurrence might have been underestimated. However, the main focus of this study was not to evaluate the tumor recurrence rate itself, but to evaluate the prognostic impact of procedure-related factors on the disease-free survival.

In conclusion, selective TACE could prolong the disease-free survival period of patients with inoperable HCC, as was shown by the multivariate analysis. A future larger scale controlled study between conventional TACE and selective TACE will be helpful to further evaluate this subject.
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