Prospective Study of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: An Asian Cooperative Study between Japan and Korea

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ABSTRACT

Purpose: To evaluate the safety and efficacy of transcatheter arterial chemoembolization used for the treatment of unresectable hepatocellular carcinoma (HCC) with an Asian cooperative prospective study between Japan and Korea.

Materials and Methods: Patients with unresectable HCC unsuitable for curative treatment or with no prior therapy for HCC were enrolled. The patients underwent transcatheter arterial chemoembolization with emulsion of Lipiodol and anthracycline agent, followed by embolization with gelatin sponge particles, which was repeated on an as-needed basis. The primary endpoint was 2-year survival rate, and the secondary endpoints were adverse events and response rate.

Results: The 2-year survival rate of 99 patients was 75.0% (95% confidence interval, 65.2%–82.8%). The median time-to-progression was 7.8 months, and the median overall survival period was 3.1 years. Of 99 patients, 42 (42%) achieved a complete response, and 31 (31%) had a partial response. The response rate was 73% using modified Response Evaluation Criteria in Solid Tumors. The grade 3–4 toxicities included increased alanine aminotransferase level in 36%, increased aspartate aminotransferase level in 35%, thrombocytopenia in 12%, and abdominal pain in 4% of patients. All other toxicities were generally transient.

Conclusions: Asian transcatheter arterial chemoembolization demonstrated sufficient safety and reasonable efficacy as a standard treatment for unresectable HCC. These results could be useful as reference data for future trials of transcatheter arterial chemoembolization.

ABBREVIATIONS

AFP = alpha fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, FAS = full analysis set, HCC = hepatocellular carcinoma, PIVKA II = protein induced by vitamin K absence or antagonist-II, RECIST = Response Evaluation Criteria in Solid Tumors

Primary liver cancer accounted for > 38,000 and 15,000 deaths per year in Japan and Korea, respectively; it is the fourth most common cause of death after lung, stomach, and colorectal cancers in Japan, and it is the third most

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common cause of death after lung and stomach cancers in Korea (1). Of all primary liver cancers, approximately 95% in Japan and 85% in Korea are hepatocellular carcinomas (HCCs), which are mostly attributable to chronic hepatitis or liver cirrhosis caused by persistent infection with hepatitis C or B viruses. Hepatitis B infection is more prevalent in Korea, whereas hepatitis C infection is more common in Japan (2). Despite these differences in etiology, the treatment strategy for HCC is the same in Japan and Korea. Curative therapies, such as hepatic resection or liver transplantation, are applicable in only a small proportion of patients because of excessive tumor invasion or poor hepatic function or both. Although local ablative therapy, such as radiofrequency ablation, has an effectiveness equivalent to that of hepatic resection for HCCs $\leq$ 3 cm in size and with three or fewer nodules, it is unsuitable for tumors $>$ 3 cm or for multiple tumors. For this stage of HCC, transcatheter arterial chemoembolization is the main therapeutic option (3–5). Transcatheter arterial chemoembolization has been shown to prolong survival significantly in several randomized controlled trials compared with chemotherapy alone (6) or conservative treatment (7–13). Meta-analyses (14,15) have also demonstrated a clear survival benefit of transcatheter arterial chemoembolization for unresectable HCC (**Table 1**).

Transcatheter arterial chemoembolization with Lipiodol (Guerbet; Roissy CdG, France) and anthracycline agents followed by embolization with gelatin sponge particles has been widely used as a practical standard treatment in Asian countries for $>$ 30 years (16). Transcatheter arterial chemoembolization was used in Asian countries long before the confirmation of its survival benefit in randomized controlled trials (6–13) because these techniques were originally developed in Japan (17–19) and spread among Asian countries. However, no prospective clinical study has been fully conducted to provide convincing data that can support this treatment. Additionally, there are many technique differences between Asian transcatheter arterial chemoembolization and transcatheter arterial chemoembolization performed in Western countries. The so-called conventional transcatheter arterial chemoembolization reported in Western studies differs from Asian transcatheter arterial chemoembolization in the details of the treatment. A prospective clinical study was conducted to evaluate Asian transcatheter arterial chemoembolization for unresectable HCC. The aim of this study was to evaluate the safety and efficacy of Asian transcatheter arterial chemoembolization with a single-arm, Japan-Korea cooperative prospective study.

MATERIALS AND METHODS

Patient Eligibility

Eligible patients for study entry had unresectable HCC that was unsuitable for curative treatments. Patient inclusion criteria were as follows: histologically or clinically diagnosed HCC excluding mixed type; no previous treatment for HCC; not a candidate for hepatic resection, liver transplantation, or local ablative therapy; hypervascular lesion showing enhancement in the early phase on computed tomography (CT) or magnetic resonance (MR) imaging with bolus contrast injection; no tumor thrombosis in the first branch or main portal vein; Eastern Cooperative Oncology Group performance status of 0–2; Child-Pugh classification of A or B; adequate hematologic, hepatic, renal, and cardiac function (leukocytes $\geq$ 3,000/mm^3, platelets $\geq$ 50,000/mm^3, serum bilirubin $\leq$ 3.0 mg/dL); age $\geq$ 20 years old; and written informed consent.

The exclusion criteria were as follows: extrahepatic metastasis; hepatic vein invasion or biliary invasion; ruptured tumor; prior biliary enteric bypass or endoscopic transampullary stent placement or percutaneous biliary drainage; clinically significant refractory ascites or pleural effusion; severe arterioportal or arteriovenous shunts in the liver; allergy to contrast medium precluding angiography; severe and active comorbidity such as heart disease or renal disease; hepatic encephalopathy or severe mental disorder; active gastrointestinal bleeding; active concomitant malignancy; pregnancy, lactation, or childbearing potential in women; and men who are sexually active and not willing or able to use medically acceptable forms of contraception. The inclusion and exclusion criteria were almost same as those in the clinical trial conducted by Llovet et al (12).

The pretreatment evaluation required a complete history and physical examination and baseline assessments of organ function. In addition, contrast-enhanced CT or MR imaging of the abdomen and x-ray or CT of the chest were performed before treatment for staging to assess the local extension of the tumor and to exclude the presence of distant metastasis.

Transcatheter Arterial Chemoembolization Procedure

Patients with unresectable HCC underwent transcatheter arterial chemoembolization using an emulsion of epirubicin or doxorubicin and Lipiodol followed by gelatin sponge injection. The dose of anticancer agents and Lipiodol used in transcatheter arterial chemoembolization was determined according to tumor size; only the maximum doses were defined in this study: 100 mg/body for epirubicin, 70 mg/body for doxorubicin, and 20 mL for Lipiodol. Epirubicin or doxorubicin dissolved in aqueous nonionic contrast medium was mixed with Lipiodol to form an emulsion using the pumping technique. The resulting emulsion had to be injected immediately. Transcatheter arterial chemoembolization was performed as follows: (i) tumor enhancement and the feeding artery were confirmed using abdominal angiography; (ii) a catheter was inserted into the feeding artery of the HCC, and the emulsion containing epirubicin or doxorubicin with Lipiodol was injected; (iii) embolization of the feeding artery was achieved using small pieces of gelatin sponge until the disappearance of tumor stain; (iv) the therapeutic effect