Transarterial Chemoembolization for Hepatitis B Virus–associated Hepatocellular Carcinoma: Improved Survival after Concomitant Treatment with Nucleoside Analogues

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ABSTRACT

Purpose: To determine whether nucleoside analogue therapy is associated with improved survival in patients with hepatitis B virus (HBV)–associated hepatocellular carcinoma (HCC) who are treated solely with transarterial chemoembolization.

Materials and Methods: A retrospective chart review of patients diagnosed with HBV-associated HCC was performed to identify patients treated solely with chemoembolization. Relevant demographic and clinical data were extracted and recorded. The influence of therapy with nucleoside analogues (lamivudine, adefovir dipivoxil, or entecavir) was determined by estimating the survival function using the Kaplan-Meier product-limit method.

Results: The inclusion criteria for chemoembolization were met by 81 patients (67 men and 14 women, mean age 60.6 years ± 9.2); 21 (25.9%) of these patients had been treated with nucleoside analogues. The number of chemoembolization treatments was significantly greater in the patients who were treated with nucleoside analogues (3.43 ± 2.32) than in the patients who did not receive nucleoside analogues (1.82 ± 0.95; $P = .0022$). The 1-year, 3-year, and 5-year survival rates were 89.5%, 66.8%, and 40.5% in the patients treated with nucleoside analogues and 72.6%, 27.5%, and 14.3% in the patients not treated with nucleoside analogues. The survival rate was significantly higher in the patients who received nucleoside analogues ($P = .0051$). Nucleoside analogue intake was an independent factor that was associated with increased survival ($P = .0063$).

Conclusions: Administration of nucleoside analogues was associated with longer survival in patients with HBV-associated HCC who were treated with transarterial chemoembolization.

ABBREVIATIONS

AFP = alpha-fetoprotein, HBV = hepatitis B virus, HCC = hepatocellular carcinoma

Transarterial embolization was initially used to treat hepatocellular carcinoma (HCC) by Doyon et al (1) in 1974, and chemoembolization with gelatin sponge particles and anticancer agents was subsequently developed in Japan to treat inoperable HCC (2). Despite the increase in the number of patients who undergo complete curative treatments such as hepatectomy or radiofrequency ablation (3), transarterial chemoembolization continues to have an important role, both as an initial treatment and as a therapeutic alternative for recurrent disease (4) because of the advanced nature of HCC at diagnosis and the high rate of recurrent disease (5). The benefits resulting from chemoembolization have long been a subject of debate (6–10), but two randomized trials found that chemoembolization was associated with higher survival compared with symptomatic treatment (4,11,12).

Because of poor liver function, patients with HCC do not always receive chemoembolization. Repeated chemoembolization treatments for HCC may cause liver function to deteriorate despite the fact that the deterioration of liver function by each chemoembolization treatment would be mild (13). If repeated chemoembolization treatments are to be used in cases of HCC recurrence, it is important to

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Tables E1 and E2 are available online at *www.jvir.org*.

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prevent the worsening of liver function in the intervals between the treatments for longer survival (14).

Nucleoside analogues against hepatitis B virus (HBV) have been used since the late 1990s to suppress the replication of HBV and to normalize transaminase levels. Therapy with nucleoside analogues against HBV is known to arrest the progression of hepatic dysfunction in patients with chronic hepatitis B. More recent studies have shown that these drugs prevent the development of liver failure, even in the patients with advanced liver fibrosis (15–19). However, it is unknown whether this beneficial effect of antiviral therapy translates into longer survival for patients with concomitant HCC who undergo chemoembolization. We conducted a retrospective review of our experiences using chemoembolization to treat HCC in patients with chronic HBV infection.

MATERIALS AND METHODS

Patients

The complete study protocol was approved by the institutional review board of our hospital and was performed in compliance with the Helsinki Declaration. Between July 1997 and December 2010, 1,359 patients were diagnosed with primary HCC at our institution. Chronic HBV infection was confirmed in 260 of these patients, and 95 of these 260 patients were treated with chemoembolization. Of these 95 patients, 14 underwent treatments other than chemoembolization for recurrent HCC (4 underwent hepatectomy and 10 underwent radiofrequency ablation), and the remaining 81 patients had been treated with chemoembolization alone for recurrent HCC tumors. Our study retrospectively examined these 81 patients.

HCC was diagnosed based on clinical criteria (20) in all 81 patients. Specifically, the patients had a pertinent clinical background (chronic HBV infection) and typical imaging results. The tumor usually was detected by B-mode ultrasonography with typical HCC imaging features, including a hypoechoic tumor or a tumor with a mosaic pattern with a halo. HCC was diagnosed when a high-density mass was detected on arterial phase dynamic computed tomography (CT) images combined with a low-density mass on portal phase dynamic CT images obtained with a single or multidetector helical CT scanner. All of the patients with possible HCC tumors underwent angiography using a unified CT-angiography system (Interventional-CT; Toshiba, Tokyo, Japan) (21,22). CT during arterial portography and CT during hepatic arteriography were also performed to evaluate the progression of HCC (23).

The patients included 67 men (82.7%) and 14 women (17.3%), with a mean age of 60.6 years ± 9.2. The liver function at diagnosis was Child-Pugh class A in 49 patients (60.5%). At the time of diagnosis, 52 patients (64.2%) had multiple initial HCC tumors. HCC was accompanied by branch portal vein invasion in 18 patients (22.2%), but no patients had HCC invasion of the main portal vein trunks or the left or right main portal vein (**Table E1**).

Chemoembolization for Hepatocellular Carcinoma and Follow-up after Treatment

The treatment decisions were based principally on the Japanese HCC treatment guidelines (24). The patients were initially assessed for their eligibility for hepatic resection and subsequent local ablative therapies, including percutaneous ethanol injection, percutaneous microwave thermocoagulation, and radiofrequency ablation. The patients who were not eligible for curative treatment with surgery, local ablative therapies, or a combination of both were offered chemoembolization. The patients with Child-Pugh class C (25) liver function and the patients with HCC invasion of the main portal vein trunks and left or right main portal vein were not offered chemoembolization. Chemoembolization was performed by injecting an emulsion of 50 mg of farmorubicin hydrochloride (Epirubicin; Adria Laboratories, Columbus, Ohio) or 100 mg of cisplatin (IA-Call; Nihon-Kayaku, Tokyo, Japan) dissolved in 5 mL of iopamidol (Iopamiron, 370 mg I/mL; Schering, Tokyo, Japan) and mixed with 5 mL of iodized oil (Lipiodol Ultra Fluid; Guerbet, Paris, France). This procedure was followed by an injection of gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Michigan). The total dose of the injected emulsion was determined by the volume of the liver that would be embolized. An unenhanced CT scan was obtained to confirm complete deposition of the iodized oil in the lesion and to complete the treatment.

After the first chemoembolization treatment, the patients were followed for 2.39–118.6 months (median follow-up period 19.3 months) at our institution with ultrasonography and CT or magnetic resonance imaging performed every 3–6 months. Serum tumor markers (alpha-fetoprotein [AFP], *Lens culinaris* agglutinin-reactive AFP, and des-gamma-carboxy prothrombin) were monitored every 3 months. When elevated tumor markers were detected, an additional imaging examination (usually CT or magnetic resonance imaging) was performed to check for recurrence or progression of HCC. If recurrence or progression was confirmed, retreatment was considered. Retreatment decisions were also based on the Japanese HCC treatment guidelines. Repeat chemoembolization was considered as a retreatment option in patients who had HCC recurrence or progression.

Statistical Analyses

The intergroup differences were analyzed using χ^2 and Mann-Whitney *U* tests for categorical and quantitative data. The date of the initial HCC treatment (chemoembolization) was defined as time zero when calculating the patient survival rates. Surviving patients and patients who died from causes other than liver disease were censored in the survival analysis. Patients whose death was caused by HCC