CLINICAL STUDY

Impact of the Interval between Transarterial Chemoembolization Sessions on Survival in Patients with Unresectable Hepatocellular Carcinoma

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ABSTRACT

Purpose: To evaluate clinical impact of different intervals between multiple transarterial chemoembolization sessions in patients with unresectable hepatocellular carcinoma (HCC).

Materials and Methods: A retrospective cohort study of 305 consecutive patients with HCC who underwent multiple sessions of on-demand transarterial chemoembolization by two independent physicians with different management policies in terms of transarterial chemoembolization interval was performed; 180 patients had intervals between the first and second transarterial chemoembolization session of < 60 days (short-interval group), and 125 patients had transarterial chemoembolization intervals of ≥ 60 days (conventional-interval group).

Results: The short-interval group had more cases of advanced-stage HCC, less favorable response to transarterial chemoembolization, and higher likelihood of having Child-Pugh class A. The short-interval group underwent more transarterial chemoembolization sessions (6.6 vs 5.5, $P = .011$), although the total number of admissions and total hospital stay were similar to the conventional-interval group. Overall survival was similar in the two groups in the full and the propensity score–matched cohorts. Although the overall survival of patients with Child-Pugh class A was comparable between the two groups in the full and propensity score–matched cohorts, the short-interval group showed inferior survival ($P = .005$) and a nonsignificant trend toward inferior survival ($P = .117$) in the full and propensity score–matched cohorts, respectively, for patients with Child-Pugh class B.

Conclusions: Transarterial chemoembolization interval did not affect survival outcomes of patients with Child-Pugh class A. A shorter transarterial chemoembolization interval showed a nonsignificant trend of adversely affecting survival for patients with Child-Pugh class B.

ABBREVIATIONS

CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, INR = international normalization ratio, mRECIST = modified response evaluation criteria in solid tumor

Transarterial chemoembolization is the most widely used treatment modality for intermediate-stage hepatocellular carcinoma (HCC) (1–3). However, transarterial chemoembolization using iodized oil has not been standardized, and its application largely depends on the clinical decision of each physician, with institutions showing variations with techniques, such as different chemotherapeutic agents (eg, doxorubicin and cisplatin); embolic materials and doses; and retreatment strategies, including differences in the interval between transarterial chemoembolization sessions (4–7).

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The interval between consecutive transarterial chemoembolization sessions is recommended to be 2–4 months in the current guidelines, whether it is performed on-demand or not (2,3). However, this recommended transarterial chemoembolization interval is not evidence based, and appropriate studies of the optimal interval between transarterial chemoembolization sessions are unavailable. Furthermore, intervals of ≥ 2 months between transarterial chemoembolization sessions may be suboptimal in terms of controlling tumor progression (7). In the present study, the clinical impact of the interval between transarterial chemoembolization sessions on overall patient survival and safety was evaluated.

MATERIALS AND METHODS

Study Subjects

This study was approved by the institutional review board of the institution, and the requirement for informed consent from the patients was waived. The study population was derived from a historical cohort of 555 consecutive patients with HCC who, in conjunction with concomitant and subsequent treatment with radiation therapy for portal vein invasion and sorafenib, underwent repeated transarterial chemoembolization sessions by two independent physicians (K.M.K., H.C.L.) with different management policies in terms of the transarterial chemoembolization schedule between January 2006 and December 2012. As a baseline study, all patients underwent four-phase dynamic computed tomography (CT), and the diagnosis of HCC was made according to algorithmic guidelines (1–3). Patients with a complete response, based on modified Response Evaluation Criteria in Solid Tumor (mRECIST), after the first transarterial chemoembolization treatment were excluded because a complete response can directly affect the interval between transarterial chemoembolization sessions (n = 132) (5,6,8,9). Patients with main portal vein invasion or bilateral involvement of the first branch portal vein (n = 57), extrahepatic metastasis (n = 54), or other concomitant malignancy (n = 7) were also excluded. Finally, 305 patients were included in the analyses and subdivided into two groups according to the interval between the first and second transarterial chemoembolization session: a short-interval group (first transarterial chemoembolization interval < 60 d) and a conventional-interval group (first transarterial chemoembolization interval ≥ 60 d).

Transarterial Chemoembolization Procedure

In accordance with the conventional transarterial chemoembolization protocol applied in our liver center (10), superior mesenteric arteriography and common hepatic arteriography were performed to assess the overall anatomy, tumor burden, and portal vein patency, based on intrahepatic HCC status assessed by hepatic dynamic CT images. Cisplatin at 2 mg/kg body weight (Cisplan; Dong-A Pharm Co, Seosan, Korea) was infused into the lobar hepatic artery for 15 minutes without an injection of embolic particles. After vascular catheterization with a microcatheter placed selectively or superselectively into the distal tumor-feeding artery, an emulsion of 2–20 mL of iodized oil (Lipiodol Ultra-Fluide; Laboratoires Guerbet, Aulnay-sous-Bois, France) and cisplatin in a 1:1 ratio was administered into the target arteries. Embolization of the arterial tumor feeders was then performed using a Gelfoam slurry (Gelfoam; Upjohn, Kalamazoo, Michigan) until arterial flow stasis was achieved. The Gelfoam slurry was made manually by cutting up a 70 mm × 50 mm × 10 mm Gelfoam sponge. There was no change in the transarterial chemoembolization protocol throughout the study period.

Principally, transarterial chemoembolization was performed on-demand (5,6,8) every 4–16 weeks if there was evidence of residual viable tumor on follow-up CT imaging. Transarterial chemoembolization was not implemented when there was no residual tumor. The decision not to perform further transarterial chemoembolization procedures was made using the following criteria: (*i*) deterioration in liver function, (*ii*) transarterial chemoembolization was considered ineffective, (*iii*) ascites worsened, (*iv*) severe vascular invasion that made additional transarterial chemoembolization impossible, and (*v*) other technical problems or contraindications for transarterial chemoembolization.

Study Outcomes and Follow-up

The primary outcome of the current study was all-cause mortality. The index date was defined as the date of the first transarterial chemoembolization session. Patients were followed up from the index date to death or the last follow-up date (August 31, 2014). Overall survival was compared for the entire study population and the propensity score–matched cohort. Thereafter, subgroup analysis was performed according to the Child-Pugh class, tumor size, and presence or absence of portal vein invasion. Four-phase dynamic CT was performed at the start and 1 month after transarterial chemoembolization, and the tumor response to transarterial chemoembolization was evaluated by mRECIST, which exhibits superior performance for determining tumor response (11,12). Dynamic CT scans subsequently were principally performed 1 month after a given course of transarterial chemoembolization for the patients with remaining viable tumors. In patients with no viable tumor on dynamic CT images after repeated transarterial chemoembolization, follow-up dynamic CT images were taken at intervals of 2–3 months until tumor recurrence was noted. The total number of transarterial chemoembolization sessions performed in each patient was recorded. To evaluate procedure-related mortality, death within 1 month after the last transarterial chemoembolization session was