Blood Neutrophil-to-lymphocyte Ratio Predicts Survival in Patients with Unresectable Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization

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ABSTRACT

Purpose: To evaluate whether the neutrophil-to-lymphocyte ratio (NLR) predicts survival in patients with unresectable hepatocellular carcinoma (HCC) before and after transarterial chemoembolization treatment.

Materials and Methods: Clinical and laboratory data for 145 consecutive patients undergoing transarterial chemoembolization for unresectable HCC during 2001–2004 were analyzed retrospectively. The NLR was recorded before and 3 days after treatment.

Results: The pretreatment mean NLR was 3.3; 59 (40.7%) patients had an elevated NLR (≥ 3.3). The median survival of patients with a high NLR was 8 months (range 1–28 months) compared with 12 months (range 2–41 months) for patients with a normal NLR; a significant difference was found in overall survival (log-rank test, $P = .001$). The NLR was increased in 127 (87.6%) patients after transarterial chemoembolization and was decreased in 18 patients; the increase indicated better outcomes (log-rank test, $P = .006$). Age (≥ 49 y), high NLR, decreased NLR after treatment, large tumor (≥ 5 cm), vascular invasion, and elevated serum α-fetoprotein (AFP) level all were predictors of poor survival. Multivariate analysis showed that a high NLR ($P = .041$) and vascular invasion ($P = .040$) were independent factors for predicting worse survival.

Conclusions: A high NLR independently predicts poor survival in patients with unresectable HCC undergoing transarterial chemoembolization treatment, and an increased NLR indicates a better outcome than a decreased NLR for patients after transarterial chemoembolization.

ABBREVIATIONS

AFP = α-fetoprotein, CRP = C-reactive protein, HCC = hepatocellular carcinoma, IL = interleukin, NLR = neutrophil-to-lymphocyte ratio, PT = prothrombin time

Survival of patients with unresectable hepatocellular carcinoma (HCC) is very poor, with a 3-year survival rate of 8%–10% (1). Few of these patients are eligible for curative resection. Transarterial chemoembolization is the mainstay therapy for unresectable HCC, and a metaanalysis of randomized controlled trials has shown that survival is improved after transarterial chemoembolization (2). Although several factors have been identified as prognostic indicators for patients with HCC, including tumor size, vascular invasion, extrahepatic spread, and serum α-fetoprotein (AFP) level (1,2), useful clinical prognostic factors were not validated in recent studies of unresectable HCC, and we cannot predict effectively the survival of patients with unresectable HCC undergoing transarterial chemoembolization.

Increasing evidence that correlates the presence of systemic inflammation with poor survival in certain cancers has been reported. The presence of a systemic inflammation response can be determined by both the expression of C-reactive protein (CRP) and the neutrophil-to-lymphocyte ratio (NLR) (3,4). Preoperative serum CRP level has been found to be associated with early recurrence and poor survival after resection for HCC (5) and colorectal cancer (3), but CRP is not routinely measured in many hospitals,

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and CRP level displays nonspecific change after treatment (6). Several studies have shown that an elevated NLR is correlated with poorer prognosis in patients with cardiovascular and peripheral vascular disease (7), gastric cancer (8), ovarian cancer (9), colorectal liver metastases (10–12), and resectable HCC (13). However, most studies focused on the profile of NLR as an indicator of systemic inflammation status before treatment, and the prognostic value in unresectable HCC is unclear. It is necessary to confirm whether the NLR is a useful prognostic factor in unresectable HCC before and after treatment.

MATERIALS AND METHODS

Patients

Patients with unresectable HCC who underwent transarterial chemoembolization at the Hepatobiliary Tumor Department between 2001–2004 were selected from a prospectively maintained hepatobiliary tumor database. The diagnosis of HCC was based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver (14). HCC was diagnosed by at least two radiologic images showing characteristic features of HCC or one radiologic image showing characteristic features of HCC associated with elevated serum AFP (≥400 ng/mL) or histopathologic evidence.

Clinical and laboratory data of selected patients were recorded, including patient age, sex, biochemical parameters, hematologic parameters, and tumor status. Biochemical data included serum concentrations of alanine transaminase, aspartate transaminase, γ-glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, albumin, and total bilirubin and the measurement of prothrombin time (PT). The results of hematologic parameters (all white blood cell and differential counts and ratios) were evaluated before and 3 days after treatment. The NLR was calculated from the differential ratios by dividing the neutrophil ratio by the lymphocyte ratio. Patients were divided into a high NLR group and a normal NLR group according to the mean level of NLR before transarterial chemoembolization. The profile of NLR change after treatment was also evaluated. This study protocol was approved by the Ethical Committee of the Cancer Center of Sun-Yat San University.

Inclusion and Exclusion Criteria

Patients who met the following inclusion criteria were enrolled for this study: *(i)* age 18–75 years, *(ii)* HCC with no previous treatment, *(iii)* Eastern Cooperative Oncology Group performance status 0–1, and *(iv)* normal liver or Child-Pugh A cirrhosis. Also, unresectable tumor had to fit at least one of the following criteria: *(i)* multiple tumors with the largest size greater than 5 cm, *(ii)* the presence of segmental (tumor thrombus in the peripheral portal vein of the second or lower order branch) or major (tumor thrombus in the first portal branch or main portal vein) portal vein tumor thrombi on imaging, or *(iii)* extrahepatic metastasis. Patients were excluded from the study if they had one or more of the following: *(i)* avascular or hypovascular tumor; *(ii)* diffuse-type HCC; *(iii)* evidence of hepatic decompensation, including ascites, esophageal or gastric variceal bleeding, or hepatic encephalopathy; *(iv)* severe underlying cardiac or renal diseases; *(v)* portal vein tumor thrombi with complete main portal vein occlusion and without adequate collateral circulation around the occluded portal vein; or *(vi)* clinical symptoms or signs of sepsis.

During the study period 2001–2004, 756 patients with HCC underwent transarterial chemoembolization at the Hepatobiliary Tumor Department. Of these patients, 544 were excluded because they did not meet the inclusion criteria or different chemotherapeutic agents were used than were required by this study. In addition, 50 patients with incomplete clinical or laboratory data and 17 patients lost to follow-up were excluded. We enrolled 145 patients who were eligible for this study. The reasons for unresectability in these 145 patients included multiple tumors (n = 81), major vascular invasion (n = 39), and extrahepatic metastases (n = 29). Each patient could have more than one reason for unresectability.

Transarterial Chemoembolization

Transarterial chemoembolization treatment was performed using techniques described previously (15,16). Visceral angiography was performed to assess the arterial blood supply of the liver after a selective catheter had been introduced. The same three chemotherapeutic agents with the same dosage were used consistently in this study, regardless of tumor number and size. Hepatic artery infusion chemotherapy was performed using carboplatin 300 mg (Bristol-Myers Squibb, New York, New York). Subsequently, chemolipiodolization was performed using epirubicin 50 mg (Pharmorubicin; Pfizer, New York, New York) and mitomycin C 8 mg (Zhejiang Hisun Pharmaceutical Co Ltd, Taizhou, Zhejiang, China) mixed with 5 mL of lipiodol (Lipiodol Ultra-Fluide; André Guerbet Laboratories, Aulnay-Sous-Bois, France). If residual flow remained after these agents were infused, additional lipiodol was injected. In some cases of large tumors in which we could not achieve stasis in a tumor-feeding artery with the maximum amount of iodized oil (30 mL), embolization was performed with absorbable gelatin sponge particles (Gelfoam; Hangzhou alc Ltd, Hangzhou, Zhejiang, China) 1–2 mm in diameter. The injection was slowed or discontinued if reflux occurred. Patients were observed carefully after treatment, and analgesia was given when necessary.

Follow-up

Posttreatment surveillance was conducted to follow up patients who had undergone transarterial chemoembolization. Patients underwent abdominal computed tomography (CT) scans during the first month after transarterial chemoembolization; liver CT scans were performed at