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Higher serum interleukin-17A levels as a potential biomarker for predicting early disease progression in patients with hepatitis B virus-associated advanced hepatocellular carcinoma treated with sorafenib

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ABSTRACT

Background: Although sorafenib is the only available drug with proven efficacy for patients with advanced hepatocellular carcinoma (HCC), the clinical efficacy of sorafenib is variable and unpredictable. The aim of the current study was to identify potential serum biomarkers predicting cancer progression and overall survival (OS) in patients with hepatitis B virus (HBV)-related advanced HCC treated with sorafenib.

Methods: Thirty-four patients with HBV-related advanced HCC (modified Union for International Cancer Control [UICC] stage IVa or IVb) treated with sorafenib for more than 4 weeks were retrospectively enrolled. Using a Luminex 200 system, 11 cytokines including interleukin-17A (IL-17A) were measured in baseline serum samples prior to sorafenib administration. Several clinical factors and the serum concentrations of the 11 cytokines were analyzed using Cox regression analysis.

Results: In the analysis of progression-free survival (PFS), older age (year; hazard ratio [HR] = 1.07; 95% confidence interval [CI] = 1.00–1.15; $P = 0.046$) and higher baseline serum IL-17A level (>1.94 pg/mL; HR = 19.96; 95% CI = 3.32–119.86; $P = 0.001$) were identified as significant risk factors for early progression with good predictive power (Harrell's C = 0.817, standard error estimates (se) = 0.085). In the analysis of OS, higher Child-Pugh score (>5; HR = 2.35, 95% CI = 1.09–5.10, $P = 0.030$) and lower serum baseline fibroblast growth factor-2 level (≤20.57 pg/mL; HR = 3.24, 95% CI = 1.22–8.60, $P = 0.018$) were identified as negative predictive factors for OS, even though the model did not have significant predictive power (Harrell's C = 0.634, se = 0.062).

Conclusion: A higher serum IL-17A level is a potential biomarker for predicting poor PFS in patients with HBV-related advanced HCC treated with sorafenib.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide [1]. Advanced HCC is commonly defined as metastatic or locally advanced HCC not amenable to locoregional therapy. In general, patients with advanced HCC show extremely poor prognosis. The median overall survival (OS) of patients with advanced HCC who receive only conservative care has been shown to be about 4–7 months [2,3]. Patients treated with sorafenib also showed a median OS of only 7–10 months [2,4].

Abbreviations: AFP, alpha fetoprotein; CI, confidence interval; DNA, deoxyribonucleic acid; EGF, epidermal growth factor; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; IFN-γ, interferon-γ; IL, interleukin; IP-10, IFN-γ-inducible protein-10; MCP-1, monocyte chemoattractant protein-1; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease; TNF-α, tumor necrosis factor-α; UICC, Unison for International Cancer Control; VEGF, vascular endothelial growth factor.

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Sorafenib is the first chemotherapeutic agent with proven efficacy for patients with advanced HCC [3]. Sorafenib inhibits HCC progression by blocking the signaling of various receptor tyrosine kinases, such as the vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor receptors, and Raf family [5–7]. Although sorafenib is a widely used treatment option in patients with advanced HCC, the objective response rate to sorafenib treatment is only 2–3% and the OS benefit is only about 3 months on average [2,3]. Owing to the fact that the clinical response to sorafenib is variable and unpredictable, reliable biomarkers for predicting the efficacy of sorafenib and the prognosis of sorafenib-treated patients with advanced HCC are urgently needed.

The majority of tumors, including HCC, develop in a setting of chronic inflammation and fibrotic tissue [8–10]. Inflammatory cytokines and chemokines orchestrate the tumor microenvironment, and it has been suggested that this inflammatory milieu could facilitate or interrupt cancer progression [8,11,12]. Several cytokines, including interleukin (IL)-17A and fibroblast growth factor (FGF)-2, have been suggested to play an important role in HCC progression and metastasis based on *in vitro* findings [13–15]. However, validation of the biologic plausibility of their actions has been insufficient in the clinical setting. In the present study, we evaluated whether those cytokines could be applied in real clinical practice as prognostic serum biomarkers in sorafenib treated HCC patients.

The goal of this study was to investigate novel prognostic serum biomarkers in patients with hepatitis B virus (HBV)-related advanced HCC treated with sorafenib. We analyzed several clinical factors and the pretreatment serum levels of 11 cytokines, including epidermal growth factor (EGF), FGF-2, granulocyte colony-stimulating factor (G-CSF), interferon-γ (IFN-γ), IL-12p70, IL-17A, IL-8, IFN-γ-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), and VEGF in order to identify biomarkers to predict the response to sorafenib and/or survival in patients with advanced HCC.

2. Materials and methods

2.1. Patient selection

This retrospective cohort study was conducted at Ajou University Hospital, Suwon, South Korea. Medical records of a total of 112 consecutive patients with advanced HCC treated with sorafenib between October 2008 and November 2012 were reviewed. Finally, 34 of the 112 patients were selected based on serum availability (within 2 weeks prior to sorafenib administration) and the following inclusion criteria: (1) age between 18 and 75 years; (2) HBV-related HCC; (3) modified Union for International Cancer Control (UICC) stage IVa or IVb cancer; and (4) treatment with sorafenib for a period longer than 4 weeks. Exclusion criteria were as follows: (1) previous history of another primary malignancy other than HCC; (2) co-infection with hepatitis C or human immunodeficiency virus; (3) history of consuming >20 g of alcohol per week; and (4) Eastern Cooperative Oncology Group (ECOG) performance status ≥2. The diagnosis of HCC was based on American Association for the Study of Liver Diseases practice guidelines [16]. Patients received sorafenib 400 mg twice daily until the occurrence of disease progression or toxicity. Once toxicity occurred, the sorafenib dose was modified according to the type of side effect and the grade of toxicity [17,18]. Patients were followed up with dynamic liver computed tomography (CT) every 2–3 months after the initiation of sorafenib administration.

Medical data including gender, age, pre-existing underlying diseases, Child-Pugh class, previous history of HCC treatment, tumor number, tumor size, vascular invasion, presence of extrahepatic metastasis, HCC stage according to the modified UICC criteria, duration of sorafenib treatment, dose of sorafenib administered, adverse event during sorafenib treatment, progression free survival (PFS), and OS were collected. Tumor response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Complete response (CR): disappearance of any intratumoral arterial enhancement in all target lesions; partial response (PR): at least a 30% decrease in the sum of the diameters of viable (arterial enhancement portion) target lesions, taking as reference the baseline sum of the diameters of target lesions; stable disease (SD): any cases that not qualifying for either PR or progressive disease (PD); and PD: increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since the initiation of treatment [19]. Adverse events associated with sorafenib treatment were monitored with the use of version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events [20]. PFS was defined as the time from the initiation of sorafenib administration to disease progression. OS was defined as the time from the initiation of sorafenib to death from any cause. Baseline laboratory data including complete blood count, total bilirubin, creatinine, albumin, alanine transaminase, prothrombin time, and alpha-fetoprotein (AFP) were collected.

2.2. Measurement of serum cytokines

Baseline serum was collected within 2 weeks prior to sorafenib administration and stored at −20 °C until cytokine analysis. On the basis of a literature review, 11 cytokines, including EGF, FGF-2, G-CSF, IFN-v, IL-12p70, IL-8, IL-17A, IP-10, MCP-1, TNF-α, and VEGF, which have been reported to play important roles in cancer development, progression, or metastasis, were selected as candidate circulating biomarkers. A Luminex 200 system (Millipore, Billerica, MA, USA), which is a flexible analyzer based on the principles of flow cytometry, was used to measure the serum concentrations of the cytokines. Each sample was run in duplicate as a batch, in a blinded fashion, and the mean value of all individual data was taken for the analysis.

2.3. Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and R software package [R version 3.2.5 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna Austria; URL http://www.R-project.org/)]. Patients were classified into two groups according to the concentrations of each cytokine (high or low). Because there was no definite clinical information regarding the cut-off values for the cytokines, binary cut-off values were determined among the 25th, 50th, and 75th percentile values of each cytokine, which were the most significant split point based on the *P* value from a Kaplan-Meier analysis. Univariate and multivariate Cox regression analyses were performed to identify risk factors associated with poor OS and early disease progression. Harrell's C-index of the Cox model was analyzed to assess the discriminatory power of the selected model. Spearman's rho was calculated to identify correlations between two continuous variables. For these exploratory analyses, a value of $P < 0.05$ was considered significant.

3. Result

3.1. Baseline characteristics and treatment outcomes

Table 1 shows the baseline characteristics of the enrolled patients and the original values of each cytokine. Study subjects