Serum MicroRNA-210 as a Predictive Biomarker for Treatment Response and Prognosis in Patients with Hepatocellular Carcinoma undergoing Transarterial Chemoembolization

Meixiao Zhan, MS, Yong Li, MS, Baoshan Hu, BS, Xu He, MS, Jianwen Huang, MS, Yan Zhao, MS, Sirui Fu, MS, and Ligong Lu, MD, PhD

ABSTRACT

Purpose: To investigate whether serum microRNA-210 (miR-210) level can serve as an indicator of prognosis and a predictor of efficacy of transarterial chemoembolization in patients with hepatocellular carcinoma (HCC).

Materials and Methods: Serum miR-210 level was measured in 113 patients with HCC before transarterial chemoembolization (t1), 3 days after transarterial chemoembolization (t2), and 4 weeks after transarterial chemoembolization (t3) and compared with 39 healthy control subjects. The correlations between miR-210 levels and clinicopathologic factors, tumor responsiveness, and prognosis were analyzed. The modified Response Evaluation Criteria in Solid Tumors assessment was conducted at t3.

Results: A higher mean baseline miR-210 level was observed in patients with HCC compared with control subjects (3.69 ± 2.04 vs 1.08 ± 0.45, $P < .001$). A positive correlation between baseline miR-210 level and tumor size ($P < .001$), vascular invasion ($P = .005$), tumor differentiation ($P = .037$), and Barcelona Clinic Liver Cancer stage ($P < .001$) was observed. Elevated baseline miR-210 level also served as an independent prognostic factor predicting poor overall survival (risk ratio, 2.082; $P = .003$). Patients who did not respond to transarterial chemoembolization had higher baseline miR-210 levels than patients who did respond to treatment (4.34 ± 1.67 vs 3.28 ± 2.15, $P < .001$). In addition, miR-210 levels increased significantly 4 weeks after transarterial chemoembolization in nonresponders (5.79 ± 2.06 at t3 vs 4.34 ± 1.67 at t1, $P < .001$), whereas no significant change was observed in responders (3.53 ± 2.20 at t3 vs 3.28 ± 2.15 at t1, $P = .116$). Lastly, an inverse correlation was identified between miR-210 change t1–t3 with the time to radiologic progression ($P < .001$).

Conclusions: Serum miR-210 may represent a novel biomarker for predicting efficacy of transarterial chemoembolization and overall survival for patients with HCC.

ABBREVIATIONS

AFP = α-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CR = complete response, HCC = hepatocellular carcinoma, miRNA = microRNA, miR-210 = microRNA-210, mRECIST = modified Response Evaluation Criteria in Solid Tumors, OS = overall survival, PD = progressive disease, PR = partial response, qRT-PCR = quantitative real-time polymerase chain reaction, SD = stable disease, TTP = time to radiologic progression

From the Department of Interventional Radiology, Cancer Center, Guangdong Provincial Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, 96 Dongchuan Road, Weilun Building, Guangzhou 510080, China. Received November 4, 2013; final revision received April 17, 2014; accepted April 18, 2014. **Address correspondence to** L.L.; E-mail: lulg@21cn.com

M.Z. and Y.L. contributed equally to this work and share first authorship.

None of the authors have identified a conflict of interest.

Table E1 is available online at *www.jvir.org*.

J Vasc Interv Radiol 2014; 25:1279–1287

http://dx.doi.org/10.1016/j.jvir.2014.04.013

Hepatocellular carcinoma (HCC) is a heterogeneous disease that responds differently to transarterial chemoembolization depending on a patient's baseline characteristics (1). Several studies indicate that the hypoxic environment induced by transarterial chemoembolization and increased level of angiogenesis owing to hypoxia play an important role in local recurrence and metastasis of HCC, diminishing the long-term efficacy of the treatment (2,3). Response assessment within first 4 weeks after transarterial chemoembolization is crucial for making therapeutic decisions and adjustments (4,5). Identifying sensitive and specific

biomarkers for stratification of patients before transarterial chemoembolization and prediction of response and recurrence after transarterial chemoembolization would facilitate the management of HCC.

Increasing evidence indicates that aberrant expression of microRNAs (miRNAs) is closely related to tumorigenesis and correlates with treatment response and prognosis (6). Circulating miRNAs in serum or plasma are detectable and are highly stable, even in the RNase-rich environment of the blood, and are resistant to harsh conditions, such as boiling, freeze-thaw cycles, and long-term storage in frozen conditions (7,8). Circulating miRNAs have been considered as novel noninvasive biomarkers for diagnosis, prediction of treatment efficacy, and prognosis in patients with cancer (7,9).

After transarterial chemoembolization, the tumor microenvironment becomes deranged with increased hypoxia, leading to an upregulation of hypoxia-inducible factor-1α (10). MicroRNA-210 (MiR-210), the most frequently upregulated miRNA in response to hypoxia, is induced by hypoxia-inducible factor-1α and plays an important role in the development and progression of many solid tumors (11,12). In HCC, miR-210 is overexpressed and mediates the migration and invasion of hypoxia-induced HCC cells (11). Ying et al (11) reported that expression of miR-210 in HCC cell lines after exposure to hypoxia was markedly increased and that this response was dependent on the duration of oxygen deprivation. A few studies have investigated the application of serum miRNAs in the diagnosis and prognosis of HCC (13,14), but none, to our knowledge, has investigated the relationship between serum miR-210 and the efficacy of transarterial chemoembolization. Given the important role of miR-210 in HCC and transarterial chemoembolization response, we performed a retrospective study and sought to test whether serum miR-210 levels can potentially serve as a predictor of transarterial chemoembolization efficacy and as a prognostic indicator in patients with HCC undergoing transarterial chemoembolization.

MATERIALS AND METHODS

Patient Enrollment and Baseline Characteristics

Between January 2009 and October 2011, 113 consecutive patients with a new diagnosis of unresectable HCC underwent transarterial chemoembolization at the Guangdong General Hospital. The diagnosis of HCC and the decision to perform transarterial chemoembolization were based on the HCC guidelines formulated by the Ministry of Health of the People's Republic of China (15). All patients had a biopsy performed before transarterial chemoembolization therapy. Inclusion and exclusion criteria are presented in Figure 1. Informed consent was obtained from all study participants. The study was approved by the ethics committee of Guangdong General Hospital.

The enrolled patients had a mean age of 54.1 years (SD, 11.6; range, 27–79 y). Approximately 70% were men. Mean tumor size was 6.4 cm (range, 1.5–16.5 cm). All patients enrolled in this study were receiving their first course of transarterial chemoembolization. Of 113 patients, 22 patients (19.5%) received only 1 course of transarterial chemoembolization, 47 (41.6%) received 2 courses, and 44

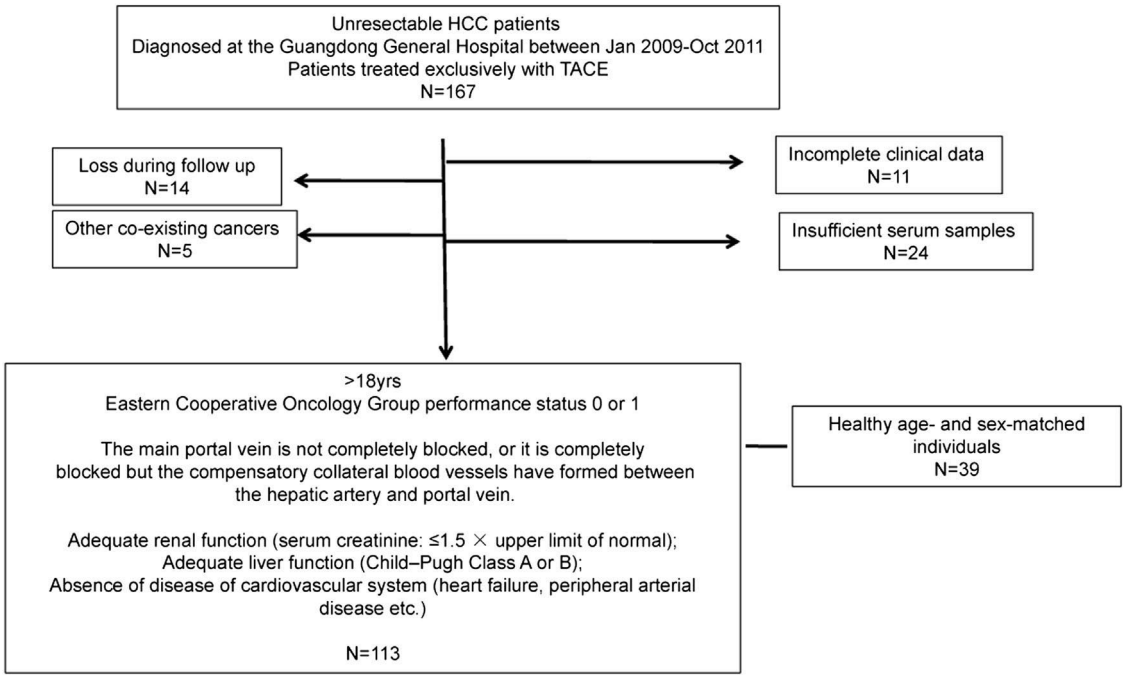

Figure 1. Flow chart of inclusion and exclusion criteria. TACE = transarterial chemoembolization.