Clinical Utility of Des-γ-Carboxy Prothrombin Kinetics as a Complement to Radiologic Response in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization

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ABSTRACT

Purpose: Serial α-fetoprotein (AFP) measurements are useful for assessing tumor responses to numerous therapies for hepatocellular carcinoma (HCC). This study tested the predictive value of changes in des-γ-carboxy prothrombin (DCP), in parallel with AFP, as an indicator of HCC response after transarterial chemoembolization.

Materials and Methods: The study group consisted of 327 patients with HCC initially seropositive for DCP (≥40 mAU/mL) and/or AFP (≥100 ng/mL) who underwent repeated chemoembolization as first-line therapy. Radiologic responses were measured based on modified Response Evaluation Criteria In Solid Tumors guidelines. Serologic response was defined as a decrease of at least 50% in DCP or AFP level from baseline. Radiologic–serologic correlation and disease progression and survival according to serologic responses were analyzed.

Results: Before treatment, 129 patients (39%) had high DCP alone, 66 (20%) had high AFP alone, and 58 (18%) had high levels of both. Radiologic and serologic responses were achieved in 88.2% and 91.4% of patients with high DCP levels and in 89.5% and 91.1% of those with high AFP levels, respectively. Serologic response based on AFP or DCP was significantly correlated with radiologic response, and this was confirmed by landmark analysis ($P < .001$). DCP and AFP responders had better times to progression and overall survival than nonresponders ($P < .001$). Cox models revealed that both serologic responses were independent estimates of survival (hazard ratios, 0.11 for DCP and 0.14 for AFP; $P < .001$).

Conclusions: After transarterial chemoembolization for HCC, DCP response may be a useful surrogate endpoint of immediate and prolonged clinical outcomes, along with AFP response.

ABBREVIATIONS

AFP = α-fetoprotein, CR = complete response, DCP = des-γ-carboxy prothrombin, HCC = hepatocellular carcinoma, HR = hazard ratio, IQR = interquartile range, mRECIST = modified Response Evaluation Criteria In Solid Tumors, OS = overall survival, PD = progressive disease, PR = partial response, SD = stable disease, TTP = time to progression

Transarterial chemoembolization is widely used for patients with hepatocellular carcinomas (HCCs) that cannot be resected or ablated, provided the lesions are confined to the liver (1). Radiologic morphology after transarterial chemoembolization is occasionally inhomogeneous and inconsistent, mainly as a result of irregular uptake of iodized oil on follow-up computed tomography (CT), and this can be a significant obstacle to imaging-based measurement of tumor response to chemoembolization (2,3). Although the amended uni- and bidimensional necrosis criteria for chemoembolization response are more predictive of survival than the conventional size criteria, results obtained with these criteria do not completely agree with actual pathologic assessment (4–6).

Quantitative measurements of α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) are simple and clinically useful methods for routine surveillance and noninvasive

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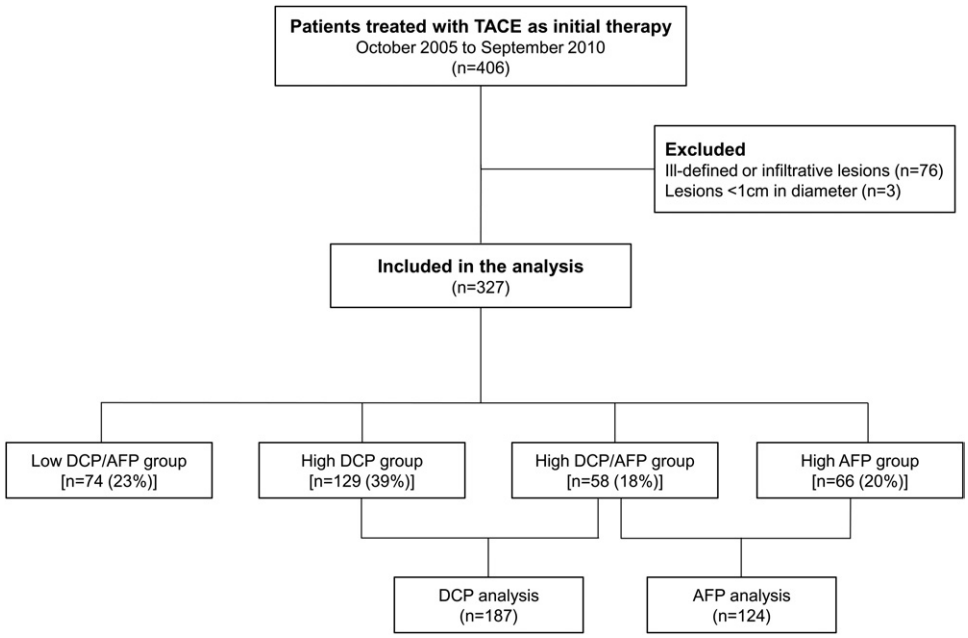

Figure 1. Diagram for patient selection.

diagnosis of HCC, as well as for evaluating prognosis and monitoring recurrence following treatment (7,8). It was recently shown that DCP levels can be associated with liver dysfunction after treatment of HCC (9), and that tumor response as measured by serum AFP is correlated with imaging-based response and predicts the ultimate clinical outcome after systemic chemotherapy and locoregional therapies, including transarterial chemoembolization (10,11).

Not all HCC tumors secrete AFP: serum AFP levels are within normal limits in as many as 40% of patients with HCC, particularly in its early stages (12,13). Moreover, in contrast to DCP, which is highly specific for HCC (14), serum levels of AFP can also be increased in patients with several nonneoplastic hepatic disorders, including acute and chronic hepatitis of any type, liver cirrhosis, and massive hepatic necrosis, which may reflect hepatic inflammatory and regenerative activity (7,15,16). In addition, serum levels of DCP are not generally correlated with AFP levels (13,17). Although it has been measured for almost 30 years, DCP has not been clearly established as the oncologic marker of choice for monitoring the response of HCC to locoregional therapy.

In light of these considerations, we have conducted an exploratory analysis to see whether serial monitoring of serum DCP could be used in conjunction with AFP measurements as a supplement to anatomic imaging for the assessment of HCC responses to transarterial chemoembolization.

MATERIALS AND METHODS

Study Population

Between October 2005 and September 2010, we used repeated transarterial chemoembolization to provide palliative first-line treatment for 406 patients with HCC without accompanying tumor extension to the portal vein, lymph nodes, or distant organs. These cases had been entered into the database of the liver center at our hospital. The HCC diagnoses were all reexamined on the basis of the updated American Association for the Study of Liver Diseases guidelines (1). Curative therapies such as hepatectomy, local ablation, and liver transplantation were not considered indicated or feasible in any of the enrolled patients. Of these patients, 76 had ill-demarcated or infiltrative HCC lesions that did not permit accurate and reproducible measurement of tumor diameter on radiographic imaging. A further three did not initially have any index lesions of 1 cm or greater in diameter with the typical radiologic features of HCC on dynamic imaging that could be selected as target lesions (18), and were therefore excluded from the data analysis (**Fig 1**). None of the patients had a history of another neoplasia, severe renal or cardiovascular disease, or uncontrolled metabolic disease, which might lead to death unrelated to the underlying liver disease or interrupt the scheduled treatment cycles. Importantly, none had experienced a hepatitis flare-up or had taken vitamin K supplements for at least 6 months before the baseline blood sample was taken, as this could affect serum concentrations of AFP and DCP. This work was approved by the institutional review board of our hospital.

Practical Chemoembolization Methodology

Signed informed consent was obtained from each patient before the start of transarterial chemoembolization. According to the routine published protocols (19), all patients underwent transarterial chemoembolization as selectively as possible by using an emulsion of a 1:1 ratio of iodized oil