Reviewer's report

Title: Prognostic Value of alpha-Fetoprotein and Des-gamma-Carboxy Prothrombin Responses in Patients with Hepatocellular Carcinoma treated with Transarterial Chemoembolization

Version: 3 Date: 31 May 2012

Reviewer: Hidenori Toyoda

Reviewer's report:

This study by Lee et al. investigated the association between the decrease in serum AFP and DCP levels after transarterial chemoembolization (TACE) and progression-free survival (PFS) and overall survival (OS) in patients with HCC and with elevated pretreatment AFP and DCP levels. The prognostic values of the dynamics of tumor markers for HCC associated with the treatment have not been fully analyzed and, therefore, the study will be of value from this aspect. I have several concerns as follows.

Major points

1. The same study group has already published several reports on similar subject (prognostic values of AFP and DCP), including reference #34 and the article recently published in European Journal of Gastroenterology and Hepatology. Did the patients studied in the present study overlap those studied in these previous studies? Are the study patients of this manuscript subpopulation of patients studied in EJGH paper? The authors should clearly describe this point and should emphasize the difference from their previous studies.

2. Because almost patients studied were infected with HBV or HCV, antiviral treatment (nucleoside analogues for HBV patients and interferon-based therapy for HCV patients) after TACE would have influenced on OS, although it would not have influenced RFS. Especially for HBV patients who were the majority of the study population, this reviewer imagines that many patients were taking nucleoside analogues. The information on these factors should be provided. In addition, in case of patients with HBV, HBV DNA levels or HBe antigen/antibody status should be included into multivariate analysis, because these factors have reportedly been associated with OS of HBV patients with HCC.

3. From the description of patient selection (page 9), they studied only patients with pretreatment elevation of both AFP and DCP. Therefore, the study focused on only a part of patients with HCC. This should be discussed. This reviewer think that patients with elevated AFP but DCP and patients with elevated DCP but AFP can be included into the study.

4. The authors analyzed the correlation of tumor marker response with WHO and mRECIST criteria (table 2), and compared their association with PFS and OS (table 3). However, they described in Method section that TACE was repeated
with 3-4 week interval based on the radiological response evaluation (they described that TACE was repeated if viable tumor remained at CT or MRI). This means that all patients achieved CR of mRECIST by TACE after treatment. Therefore, it is not appropriate to use objective response by mRECIST to see correlation with tumor marker response or to compare it with tumor marker response for prediction of PFS or OS.

5. In table 1, information on the size of tumor should be included. In addition, the number of tumors should be presented as a continuous variable. These factors should be included in multivariate analyses as factors analyzed.

6. As the authors described in Discussion section (page 21 last part), AFP elevation was frequently observed not only by HCC but also associated with the elevation of ALT. Therefore, AFP response could be poor in patients with persistently elevated ALT. In addition, patients with persistently elevated ALT are reportedly associated with poor OS due to more rapid impairment of the liver function. This should also be discussed.

Minor points

1. Abstract, page 5, Methods: AFP or DCP response was defined as a reduction of more than 50% from the baseline level 1 month after TACE. Why did the authors evaluate post-TACE tumor markers 1 month after treatment? Was it based on the half-lives of these tumor markers? Please provide the rationale for this timing of measurement.

2. Abstract, page 5, line 16: “gamma-glutamyltransferase” should be “gamma-glutamyltranspeptidase”.

3. Introduction, page 7, lines 11-12: “Recently, the national comprehensive cancer ....” Reference should be provided for this.

4. Introduction, page 8, lines 3-9: This part is not necessary and can be deleted.

5. Patients and Methods, page 10, line 2: From this description, there were no patients with HCC less than 1 cm in diameter in study population. Was this true?

6. Statistical analysis, page 12: The factors analyzed in multivariate analyses should be listed here.

7. Results, page 16, lines 5-10: “baseline albumin level was identified as an independent predictor of discordance ....” The result of multivariate analysis on this should be presented as a supplemental table. The Kaplan-Meier curves of tumor marker responder/non-radiologic responder and non-tumor marker responder/radiologic responder for PFS and OS should be presented as a supplemental figure. In addition, Kaplan-Meier curves of tumor marker responder/radiologic responder and non-tumor marker responder/non-radiologic responder should also be presented. Were PFS and OS of tumor marker responder/non-radiologic responder and non-tumor marker responder/radiologic responder similar with tumor marker responder/radiologic responder or
non-tumor marker responder/non-radiologic responder?

8. Discussion, page 17, lines 10-11: “whereas radiologic response was not significant in predicting PFS and OS.” It is normal because TACE was repeated if viable HCC remains by radiologic evaluation.

9. Discussion, page 18, lines 13-18: This part should be described in Results section with multivariate analysis presenting supplemental table and figure.

10. Discussion, page 21, line 6: “because of their medical condition” Please provide details.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.