Reviewer's report

Title: Expression and prognostic value of circulating angiogenic cytokines in pancreatic cancer

Version: 1 Date: 20 March 2011

Reviewer: Hayato Fujita

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Comments to the Authors

In this study, the Authors examined the circulating angiogenic cytokines (CACs) in patients with pancreatic cancer and the association of CACs with lymph node metastases and patient prognosis. They found that higher levels of all CACs in the serum except for PIGF significantly correlated with incidence of nodal metastasis. Although they found significant correlation between high serum levels of PDGF-AA and poor prognosis, serum levels of PDGF-BB, VEGF, and Ang-1 revealed inverse correlations with patients’ outcome.

This study is interesting and the new message is the correlation between serum levels of CACs and lymph node metastasis/prognosis. However, the paper lacks some important information and weakness consists on the long time enrollment. The manuscript would be improved by several modifications and the addition of a few statistical analyses.

Major Compulsory Revisions

1. The Authors aimed to predict patients’ prognosis by measuring the serum concentration of CACs, including VEGF, VEGFR-1, PIGF, PDGF-A, PDGF-B, Ang-1, and EGF. However, there have been accumulating evidences demonstrating the correlation between tumor angiogenesis and other soluble factors, including growth factors and chemokines (e.g., TGF-#, FGF, and HGF), in pancreatic cancer. The Authors should mention about the reason why they selected these seven markers or why they excluded other markers in the Introduction section.

2. Before assessing the correlation between the serum levels of CACs and clinicopathological factors or patients’ prognosis, the assessments of the angiogenic status (e.g., immunohistochemical analysis of CD31 or CD144) in the primary tumor and their correlation with these CACs are required. Furthermore, the assessments of vessel invasion of cancer cells in the primary tumor and their correlation with serum CACs levels may provide significant impact.

3. Although the Authors are discussing about the correlation between angiogenic cytokines and response or resistance to chemotherapy (Discussion section, third paragraph), the present study lacks the assessment of relationship between adjuvant chemotherapy and the levels of CACs. Moreover, adjuvant chemotherapy status should be added to univariate and multivariate survival
analyses. Additionally, the information of adjuvant chemotherapy regimens should be supplied in the Materials and Methods section, including the number of patients receiving respective treatments. Also, the analyses of disease-free survival should be added, because this study includes the patients receiving adjuvant chemotherapy.

4. For better understanding, box-plot or dot-plot graph presentation is recommended for Figure 1. Additionally, graph presentation of correlation between the serum levels of CACs and lymph node metastasis may provide impacts (Table 3).

5. Tables 1 and 3 lack some important information. The Authors should provide the data evaluating the correlation between the serum levels of CACs and other major clinicopathological factors (e.g., Adjuvant chemotherapy, Radiotherapy, UICC Stage, and neural invasion).

Minor Essential Revisions
1. In Figure 2, the labels of each group and the number of patients in each group should be added. Also, the statistical P-value should be provided in each Figure or their Figure legends.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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.