Reviewer's report

Title: Platinum sensitivity and CD133 expression as risk and prognostic predictors of central nervous system metastases in patients with epithelial ovarian cancer

Version: 5
Date: 29 June 2014

Reviewer: Tsukasa Baba

Reviewer's report:

This article by Liu et al. demonstrates following findings through an analysis of 29 epithelial ovarian cancer (EOC) cases with CNS metastases-

1. Extent of surgical excision and platinum sensitivity of EOC are associated with time to develop CNS metastases and
2. CD133+ cluster formation in CNS metastases and application of multimodal treatment are respectively prognostic factors

They analyzed a pretty large cohort with more than 1300 EOC patients, which would provide a clinically significant evidence although it was a single-institute retrospective study. As for the 1st issue, these two are general prognosis predictive factors as authors described. Brain metastasis is itself very rare, but in this context, it appeared one of consequent recurrent places resulting in reasonable poor outcome in those with CNS-metastasis. And a systematic review for 591 patients bearing brain metastasis from EOC was already published by Pakneshan et al., and the efficacy of multimodal treatment has been reported in several reports. Thus, this reviewer should state that the findings authors confirmed are valuable but not novel in terms of the significance to provide a new implication in the management of EOC.

Authors mentioned the facts that cisplatin was not able to overcome the blood-brain-barrier, and that CNS-metastasized tumors mainly consist of lung or breast cancers. Readers including this reviewer would like to know the potential markers in primary EOC to indicate future cisplatin-refractory CNS-metastasis. The marker might be one of molecules or transcriptional factors (TF) associated with aggressive features of breast cancer or lung cancer. In this genome-wide analysis era, several datasets of breast cancers and lung cancers consisted of cases with or without CNS-metastasis are published and available, which should make authors able to mine candidates through genome-wide analysis. Among the 29 EOC cases with CNS-metastasis, both primary tumor and CNS-metastasis should be available for immunohistochemical-staining in 19 cases as they did for CD133-staining. If the authors successfully exhibited the up-regulated expression of candidate molecules/ TF in these pairs compared with those without CNS-metastasis, a future prospective study can be conducted for picking up cases which needs close observation for CNS-metastasis.
CD133 expression in EOC was introduced as a “stem-ness” marker in Background part and Discussion part, but the interpretation of CD133+ population in the cell cluster of CNS-metastasis was not enough in the aspect of enrichment of cancer initiating cell. Previous reports demonstrated enrichment of cancer initiating cells in metastatic site or recurrence tumors. The result that all nine CD133+ cases exhibited CD133+ cluster in CNS-metastasis did match previous reports, but half cases did not exhibit CD133 in primary tumors. Was there no tumor initiating cells in such cases? Authors stated CD133- cells also had potency of tumor progression. Recent reports emphasized the necessity to assess the stem-ness with several markers with such as CD44, ALDH, EpCAM as well as CD133. If authors did not employ CD133 as a simple marker to predict prognosis but a stem-ness marker, authors should deepen their interpretation of their result or conduct immunostaining of other markers for strengthening the analysis of stem-ness.

To my regret, this article in the current version is not novel enough to be published in this journal. However, if authors would deepen their study in the context to seek for a novel marker, this article should beblushed up as they have more than 1300 clinical samples. This reviewer would be happy to review the revised article with updated data again.

**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.