Reviewer's report

Title: TP53 status and taxane-platinum versus platinum-based therapy in ovarian cancer patients: a non-randomized retrospective study.

Version: 1 Date: 11 August 2007

Reviewer: angiolo gadducci

Reviewer's report:

General

-------------------------------------------------------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The authors investigated the clinical, pathological and biological variables related to response to taxane/platinum-based chemotherapy as well as to platinum-based chemotherapy in patients with advanced ovarian cancer. This issue has a strong clinical relevance, also taking into consideration the different results of the four major randomised trials comparing these chemotherapy regimens.

It is well known that p53 gene inactivation has been found to confer resistance to cisplatin and other DNA-damaging agents. Conversely, recent clinical studies reported that patients with mutant p53 tumors were responsive to paclitaxel/platinum-based chemotherapy. The mechanism of action of taxanes consists of alterations in microtubule function and the presence of a functional p53 gene does not seem to be required for apoptotic cell death induction by antimicrotubule agents. Furthermore, pharmacological studies support the notion of increased sensitivity to taxanes by mutant p53 cells, due to the accumulation of treated cells in the G2-M phase.

In the present paper, as for the patients with TP53+ tumors, the better clinical outcome for those who received taxane/platinum-based chemotherapy is consistent with literature data. However, some questions should be taken into consideration.

1) Epithelial cancers comprise different histological subtypes that appear to be associated with distinct morphologic and molecular alterations. High-grade serous and undifferentiated carcinomas frequently show p53 mutations and dysfunction of BRCA1 and/or BRCA2 genes, whereas low-grade serous carcinomas probably develop via activation of the RAS-RAF signaling pathway secondary to either RAS or RAF mutations. Mucinous carcinomas arise via an adenoma-borderline tumor-carcinoma sequence with KRAS mutations, whereas low-grade endometrioid carcinomas develop from endometriosis via mutations in the genes encoding beta-catenin and PTEN. Although the morphologic data strongly support an origin of clear cell carcinoma from endometriosis, there are
limited data on the genetic alterations in these rare tumors. Since different histological subtypes are associated with distinct molecular profiles, it is reasonable to conceive that different molecular pathways may strongly influence the responses to different drugs. Therefore, studies investigating the correlation between p53 gene status and response to any kind of chemotherapy regimens should include patients homogenous for histological type ( i.e, patients with serous ovarian carcinoma).

2) The immunohistochemical detection of p53 accumulation may be misleading in judging p53 gene status. P53 status should be determined by polymerase chain reactions and direct sequencing of the exons 4 - 9 . For instance, also polymorphism at codon 72 in exon 4 appears to influence the response to treatment

3) As for residual disease, tumor size < 1 cm (and not < 2 cm) should be considered as a cut-off value for optimal cytoreduction.

4) It is difficult to explain why taxane –platinum therapy is of high efficacy in moderately differentiated tumors but not in poorly differentiated tumors.

---

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

---

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests