Author's response to reviews

Title: Residual neurotoxicity in ovarian cancer patients in clinical remission after first-line chemotherapy with carboplatin and paclitaxel. The Multicenter Italian Trial in Ovarian cancer (MITO-4) retrospective study.

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Author's response to reviews: see over
Reviewer 1 (Gini Fleming)

Major Compulsory Revisions

1. It is not clear in the abstract or elsewhere in the manuscript, how it was decided what grade of neuropathy the pt had during treatment. Was this taken from data collected at the time of treatment (e.g. study forms for pts on trial and clinic notes for pts off trial? And is recording that sort of information fairly standardized for off-trial pts at Naples?) or were pts asked to retrospectively state how bad their neuropathy was during treatment?

The presence and grade of neuropathy during treatment was evaluated by the investigators (study forms for patients on MITO-1 trial and clinic notes for patients off trial). The 19 patients not included in the MITO-1 study were evaluated during treatment with the same criteria used for the patients in the trial. Also residual neurotoxicity at the time of follow-up visit for this study was evaluated and graded by the visiting physician. The only information retrospectively collected and reported by the patients themselves was the time to resolution of neurotoxicity, if toxicity had resolved before the follow-up visit.

We have clarified these concepts in the Methods section of the manuscript: “Information about neurotoxicity experienced by the patients during the treatment was collected from the database of the MITO-1 trial for 101 patients, and from clinical files for the remaining 19 patients treated outside the trial. Residual neurotoxicity was evaluated by the physician and graded according to the NCI-CTC criteria, version 2.0 [5].” “Follow-up data were collected between May and September 2004. After performing a clinical examination and an interview, the participating investigators completed a dedicated case report form for each patient, reporting the grade of the eventually residual sensory and/or motor neurotoxicity.

2. Similarly, was the date of resolution of neuropathy taken by pt history? Or from case-report f/u forms?

The date of resolution of neuropathy was reported by the patients themselves at the time of the follow-up visit, when the information about neurotoxicity has been collected by the investigator and reported in a dedicated case-report form. Of course we recognize that no prospective follow-up of the neurotoxicity was planned, and this is a weakness of our study. However, we have already specified in the title, in the abstract and in the Methods section of the manuscript that this is a retrospective study, with all its limitations. However, we have clarified this concept in the Methods section: “For those patients who had experienced neurotoxicity during chemotherapy but had no residual neuropathy at the moment of the interview, the investigator reported the date of resolution of neuropathy, as referred by the patient.”

3. It should be stated somewhere that this was an human-subjects-committee-approved protocol and subjects gave appropriate consent, or that this was considered exempt by the local human subjects protection committee…

This was a retrospective study, without experimental action on the patients, so a specific approval by the Ethics Committee was not required by the Italian law. Of course, all the patients participating in the MITO-1 trial (evaluating the consolidation treatment with topotecan) gave a written informed consent before any study procedure. The other 19 patients received first-line treatment with carboplatin and paclitaxel as part of the standard clinical practice at the National Cancer Institute of Naples.

As suggested by the Reviewer, a sentence has been added to the Manuscript.

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Minor Essential Revisions

1. There are some wording errors which should be corrected. For example, in the abstract, under “Methods” “patients have been enclosed in this study” would be better said “patients were included in this study”, or “registered to this study”
OK.

p 4 ”these pts were considered in this study” might be “these pts were eligible for this study”
OK.

Discretionary Revisions

Although there was very little high-grade neurotoxicity in this study, it would be of interest to know if initial grade of neuropathy predicted for slower resolution (as would be expected)

We appreciate this suggestion.

As correctly said by the Reviewer, numbers in our study were too small to draw conclusions about relationship between initial grade of neuropathy and time to resolution. Patients with grade 1 sensory neurotoxicity were 51, and patients with grade 2 or higher were 14 (as reported in Table 1 of the manuscript).

However, following Reviewer’s suggestion, we decided to add this analysis to the manuscript. The following curve shows the time to resolution of toxicity for patients according to neurotoxicity grade. Six-months probability of residual neuropathy is 27.1% for patients with grade 1 neurotoxicity at the end of chemotherapy and 33.3% for patients with grade 2 or more. 1-year probability of residual neuropathy is 23.7% and 33.3%, and 2-year probability is 19.7% and 22.2%, for patients with grade 1 and grade 2 or more, respectively. Difference of time to resolution among the two groups of patients was not statistically significant (p=0.716, Log-rank test).

The figure has been added to the Results section, together with the following sentence:
“Figure 3 shows the time to resolution of neurotoxicity according to its severity. Six-months probability of residual neuropathy was 27.1% for patients suffering from grade 1 neurotoxicity at the end of chemotherapy and 33.3% for patients with grade 2 or more. 1-year probability of residual neuropathy was 23.7% and 33.3%, and 2-year probability was 19.7% and 22.2%, for patients with grade 1 and grade 2 or more, respectively. Difference of time to resolution among the two groups of patients was not statistically significant (p=0.716, Log-rank test).”

The following sentence has been added in the Discussion: “It should be noted that probability of long-term persistence of neurotoxicity was not negligible not only for patients with moderate or severe toxicity during chemotherapy, but also for those patients suffering from grade 1 toxicity.”
Reviewer 2 (Maurie Markman)

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
No major compulsory revisions

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
No minor essential revisions

Discretionary Revisions (which the author can choose to ignore)
No discretionary revisions
Reviewer 3 (Paul Sabbatini)

Major Compulsory Revisions:
The work of Vasey et al. JNCI 17(22) 1682-91 could be referenced, and can be incorporated into the discussion as it represents one of the few large prospective studies with validated neurotoxicity instruments that can help establish a baseline with paclitaxel and carboplatin.

We thank the reviewer for the suggestion. Actually, the randomized phase III trial of the Scottish Gynaecological Cancer Trials Group was already cited in our manuscript, as a previous publication (reference 10: Vasey PA: Role of docetaxel in the treatment of newly diagnosed advanced ovarian cancer. J Clin Oncol 2003, 21(Suppl 10):136-44). Reference has been updated according to reviewer's suggestion. Furthermore, a sentence has been added to Discussion: “In the phase III randomized trial performed by the Scottish Gynaecological Cancer Trials Group, comparing the combination of carboplatin and docetaxel with the standard carboplatin/paclitaxel combination, health-related quality of life was one of the secondary end-points of the study [10]. Coherently with the higher incidence of neurotoxicity in the carboplatin/paclitaxel arm, quality of life scores related to neurotoxicity deteriorated more in this arm, and patients treated with carboplatin/paclitaxel reported significantly worse scores for acute, persistent and long-term (6-months after treatment) neurotoxicity. These data, together with our results, emphasize that the risk of residual long-term neuropathy should be weighted with the potential benefit of adding paclitaxel to carboplatin in the re-treatment of these patients.”

With regards to the abstract:
The introduction and methods should state where the patient cohort in this retrospective study comes from and how selected.

A sentence has been added in the abstract: “120 patients have been enclosed in this study (101 participating in a multicentre phase III trial evaluating the efficacy of consolidation treatment with topotecan, and 19 treated at the National Cancer Institute of Naples after the end of the trial).”

The results section should be clarified. There is a “23% rate of residual neurotoxicity” at the “most recent followup (which is at a median of 18 months)”, yet a “15% rate of neurological toxicity 6 months after the end of chemotherapy”. Is this congruent? It gets worse over time?

Data are congruent, because the 23% rate of residual neurotoxicity at the most recent follow-up is calculated with the 60 patients experiencing toxicity during chemotherapy as denominator. The 15% rate of neurological toxicity at 6 months after the end of chemotherapy, as specified in the Methods section, is calculated with the Kaplan-Meier product limit method, that takes into account all the 120 patients analyzed. According to this analysis, the time to resolution for those patients without toxicity during chemotherapy has been considered at time 0 (end of chemotherapy), and the 5 patients without follow-up information have been considered as censored at time 0.

However, we have clarified the sentence, both in the abstract and in the results. “The remaining 14 out of 60 cases (23%) had some grade of residual neuropathy at the moment of assessment. [...] Considering all the 120 patients who received combination chemotherapy with carboplatin and paclitaxel, the probability of neurological toxicity for a patient was 54% during chemotherapy, 15% at 6 months after the end of chemotherapy, 14% at 1 year after the end of chemotherapy and 11% at 2 years after the end of chemotherapy”
With regards to the manuscript:
The Vasey reference could be added in the introduction to help set the expected baseline during treatment.
As already specified, the Vasey reference has been added to the introduction, to the discussion and in the references. In the Introduction, this reference has been added to the references regarding the incidence of neurotoxicity during first-line chemotherapy with carboplatin and paclitaxel.

In patients and methods: How was the neurotoxicity data collected in the original trials? Patient self assessment? Instrument? Physician scored? And when patients came for the followup visit, was it a physician assessment only?
In the MITO trial, and also for the 19 patients treated at the National Cancer Institute of Naples after the end of the MITO trial, neurotoxicity during the treatment was not self-assessed by the patients, but was evaluated and scored by the physician. This has been better specified in the Methods: “Neurotoxicity experienced by the patients during the treatment was taken from the database of the MITO-1 trial for 101 patients, and from clinical files for the other 19 patients treated outside the trial. Residual neurotoxicity was evaluated by the physician and graded according to the NCI-CTC criteria, version 2.0 [5].”
As for the follow-up visit, it was already specified in the Methods section that “after performing a clinical examination and an interview, the participating investigators completed a dedicated case report form for each patient, reporting the grade of the eventually residual sensory and/or motor neurotoxicity. [...] For those patients who had experienced neurotoxicity during chemotherapy but had no residual neuropathy at the moment of the interview, the investigator reported the date of resolution of neuropathy. ”

“Details of the pharmacologic treatment for neuropathy” were collected. What about this in results? There is no further mention in the manuscript. Were treatments given? Did they make a difference?
We agree with the Reviewer comment. Details of pharmacological treatment have been added in the Results and discussed in the Discussion. Coherently with the absence of treatments of proven efficacy, all patients but one did not receive any treatment for neurotoxicity. For one patient, treatment with gabapentin and corticosteroids was reported. The following sentence has been added to the Results: “No specific pharmacologic therapy for neurotoxicity was delivered, with the exception of one patient who received corticosteroids and gabapentin.”

The conclusion discusses a variety of pharmacologic interventions not tested here (see above). One might move this to the discussion only if there are no results to report. See response to previous point.
The following sentence has been added to the Discussion: However, as confirmed by the finding that only one patient in our study received a pharmacological treatment for neurotoxicity, none of these drugs is used in clinical practice.

In results, last paragraph, the “probability of neurologic toxicity” was 14% at 1 year, and 11% at 2 years. Is this congruent with numbers reported in the abstract? It would also be helpful to consistently define neurological toxicity as GI and G II separately from G III as they have important clinical implications.
Please see response about the data in the abstract. The probability of neurological toxicity (14% at 1 year and 11% at 2 years) is calculated according to the Kaplan Meier method. As already specified, we have better clarified this in the Results. Analysis of time to resolution of toxicity was asked also by Reviewer 1, and we have decided to add this information in the Results, with a comment in the Discussion. Due to small numbers, G II (13 cases) and G III (1 case) have been considered together versus G I.

In the Discussion, it would be interesting to include the concept of consolidation as another area for which neuropathy might need to be considered. (Markman et al J Clinical Oncology JCO: 2460-2465.2003).

We thank the Reviewer for this suggestion. A sentence has been added in the Discussion: “Furthermore, also the debated maintenance strategy, with the extended administration of paclitaxel after complete response to first-line chemotherapy, supported by the study of Markman et al. [13], can be seriously limited by the persistence of residual neuropathy.” Markman’s reference has been added to the references.