March 11, 2019

Dear editor:

Thanks for the detailed review and instructive comments. Below, please find a point-to-point response to the reviewer's comments

SPECIFIC COMMENTS TO AUTHORS

This is a retrospective report of a small series of patients with ovarian cancer receiving IP chemotherapy post neo-adjuvant IV chemotherapy or with adjuvant IV chemotherapy in a community center. Some specific comments to improve the manuscript:

The title of the report is misleading as both adjuvant and neo-adjuvant IV chemotherapy patients are included and authors attempt to draw comparisons between them.

The title has been changed, and we added "or have not" to the title.

- In results line 6-8 it is mentioned that patients had a stage II or III cancer. However in table 1 it is mentioned that 2 patients had stage IV. Authors should review and correct.

Corrected. We added the information to paragraph 1 of the result on page 7.

In addition, it should be discussed why an IP approach was selected in patients with extra-abdominal disease.

Two patients had stage IV disease at diagnosis, one had cytology positive pleural effusion which was drained and did not recur after neoadjuvant chemotherapy, and another patient had a malignant umbilical nodule which was resected during surgery. Since there was no other sites of metastatic disease at the time of treatment, they were offered IP treatment. This description was added to paragraph 1 of the result on page 7-8.

- Chemotherapy regimens use as described in table 3 should be further detailed i.e. with exact doses and schedules. As it stands the table is not very informative.

We recounted the data and updated Table 3 with dose and schedule.

I think that there is a lining error also in the table. The "others" regimen should be mentioned instead. What no IV means? Patients had oral chemotherapy?

The lining error is corrected and Table 4 is revised.

"Other" line is removed, and exact chemo regimens are listed.

"No IV chemo" means that those patients did not receive IV chemo treatment; they only received IP chemotherapy instead. It is explained in Table 4 now.

- Number and other information on subsequent lines of therapy should be provided. Of particular interest would be the use of bevacizumab or PARP inhibitors.

We examined the information on the subsequent lines of therapy at recurrence, but the data has a very high variation in dose and schedule, so we did not include here. Bevacizumab was not used for maintenance in any case, and it was used in 50% of the patients when they developed progression of disease, the percentage was 52% in group 1 and 46% in group 2. This data is added to Table 3. Only one patient with BRCA 1 mutation at the time of recurrence received PARP inhibitor, and this information is added to the result, page 10.

- Regarding the patient with an endometrioid cancer (page 9), it is not clear why she was counted as a recurrence if histologies were clearly different. Instead the hysterectomy specimen should be reviewed for occult primary and counted as a second primary, even no endometrial primary is found.

A though examination by the pathologist was done and reportedly they did not find endometrial primary. However, as the patient had TAH and BSO, there should not be any endometrial tissue left after surgery. We have discussed the issue among the doctors in the treatment team, and with the pathologist and among the authors. It was felt that there are 2 possibilities. The patient may have had endometriosis, with occult ectopic endometrial tissue from which endometrroid carcinoma developed. Alternatively, the patient may have had primary peritoneal carcinoma, or ovarian cancer, with occult mixed endometriod and serous histology in the primary tumor, which then recurred. We favored the second possibility. In order to error on the side of not overestimating the effect of IP chemo, we treated it as a recurrent event for calculating PFS. We added brief explanation on page 11.

- *Information on Ca125 and ascites should be included in table 1 if available.*

In response to this comment, we think that a comparable baseline would be a time point after surgery, before starting adjuvant IV and IP chemo in either groups. We specified that a CA125 value taken between 2 weeks before starting the chemotherapy and the day of starting chemo should be used as a baseline value. This information is added to Table 1.

We did not have a CT to document whether there was ascites after surgery in almost all the cases.

- *It should be clarified whether BRCA mutations in table 1 refer to somatic or germline or both.*

At the time of the study, it was not routine practice to test for somatic mutations. Therefore, all reported mutations were germline mutations. We specified that in Table 1 and 5.

Specific information on these patients such as specific type of mutation, whether in BRCA1 or BRCA2 and response to IP treatment would be of particular interest.

A new table has been added, Table 5

- It is reported in table 4 that only one patient had catheter problems. This should be further commented as in phase 3 trials about 20% of patients had significant problems leading to discontinuation. Given that the main cause of not adopting more widely the IP approach is its invasive nature and impracticality this is of importance. Authors should further describe whether a specific type of catheter was used and any specific strategies used for maintenance and use of the catheter.

Discussion was added to the section of Discussion on page 12. However, we do not think we did anything extra. We followed a protocol from MSKCC, and nurses were all in-serviced. We are not able to get the info for the specific type of catheter used over the past years in the study, as the surgeon has retired.

- For the survival analysis, the number of patients lost to follow up should be reported.

Ten patients were lost for follow up for OS calculation and 4 patients were lost for follow up for PFS calculation, and this information was added to the result on page 10.

- The practice of prophylactic hydration is of interest. Adverse effects outcomes in those patients especially regarding prevention of renal injury should be reported. In addition, the criteria to order prophylactic hydration are of clinical interest (e.g. age, comorbidities).

Prophylactic hydration was the routine practice with one physician, and was scheduled for every patient on day 4 or 5 and day 11 or 12. All three patients who suffered from renal injury were in the neoadjuvant group. Two of the 3 patients who were found to have renal insufficiency were found on the day of planned hydration, and improved after hydration. In those patients who did not have planned hydrations, this transient change could be missed thus underdiagnosed.

Sincerely,

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