Peer Review File

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Review Comments

Reviewer A

A reasonable review but the conclusion to consider high dose chemotherapy in selected patients with mediastinal germ cell tumours is too bland. There is no clear role for it in untreated patients.
Comment 1: I would be cautious about the term immature teratoma - it should be avoided stick to non-seminoma or seminoma or teratoma.

Reply 1: OK, we removed it from that part of text to avoid possible misunderstandings
Changes in the text: see lines 63-64 "…is a curative approach for teratoma, whilst for seminoma and non-seminoma…"

Comment 2: Line 83 - talks about actinomycin D being no longer used but then quotes a contemporary series (35) where it is used.

Reply 2: Thank you for this observation; as a matter of fact, except from this case series (Shamash et al) in which the regimen that the clinicians used was conceived in 1997, actinomycin is no longer used. However, to avoid internal inconsistence, we removed this drug from the period.
Changes in the text: see line 90 "…toxic drugs that have been abandoned over time"

Comment 3: Line 96- cannot make less of cisplatin- you mean the dose of cisplatin cannot be reduced any further.

Reply 3: We hope to have clarified this concept by modifying the period in the text.

Changes in the text: see line 103: "SDCT regimens have cisplatin as their main drug, despite short- and long-term toxicities associated with it".

Comment 4: In the relapsed section I would mention the paper by Badreldin et al (BJUI 2016) as it is not based on cisplatin, but the mediastinal Germ cell tumours did relatively well.

Reply 4: Thank you for the comment; we added it in the relapsed section.
Changes in the text: see lines 196-200: "A different strategy consists in administering IPO (irinotecan, paclitaxel and oxaliplatin) followed by HDCT in GCT patients who relapsed after two prior lines of cisplatin–based CT or MGCT patients who relapsed after first-line cisplatin-based treatment, as reported by a retrospective analysis; interestingly, among the 72 patients included in this analysis, 13 had MGCT, showing similar outcomes to the overall analyzed population"

Comment 5: Mention should be made of the fact that patients with mediastinal masses only may have a relatively good outcome - even with significantly raised markers and the fact that surgery may be undertaken without normalisation of markers. Possibly use tables to show results of the various phase 2 studies.

Reply 5: Thank you for this observation; we added a new reference (Radaideh et al Ann Oncol 2010)
Changes in the text: see lines 65-67 "it should be mentioned also that the outcome following resection for patients with primary nonseminomatous MGCTs could be good despite the presence of rising serum tumor markers (STMs)"

Reviewer B

Mediastinal germ cell tumors are a rare but important malignancy as they typically occur in otherwise young and healthy patients. Malignant mediastinal non-seminomas, in particular, are a challenging subset with an overall poorer prognosis as compared to their testicular counterparts. I therefore congratulate

the authors on an excellent review of the topic regarding optimal chemotherapy regimens; however, I believe a few of their comments are debatable.

Comment 1: Line 62 states: "Surgery performed through an complete en-bloc excision is a curative approach for mature teratoma, whilst for immature teratoma, seminoma, and nonseminoma it should be considered in the case of residual masses after chemotherapy". First, I don't believe that immature teratoma has been shown sensitive to cisplatin-based chemotherapy and surgery alone recommended in these cases. Secondly, any residual mass after chemotherapy for pure mediastinal seminoma typically represents complete tumor necrosis and observation alone recommended. Surgery can however be considered for very rare cases of residual mass growth in the face of normal serum markers during follow up. Second-line high-dose chemotherapy and radiation therapy are also potential options in these situations.

Reply 1: Thank you for these observations. We removed immature teratoma from this period and we modified it according to your comments.

Changes in the text: see lines 63-65 "Surgery, performed through a complete en-bloc excision, is a curative approach for mature teratoma, whilst for immature teratoma, seminoma and non-seminoma it could be an alternative to observation only (or to second-line high-dose chemotherapy or to radiation therapy) in ~~the~~ selected cases of residual masses after chemotherapy".

Comment 2: Lines 260 and 266 suggests that HDCT is a reasonable alternative to SDCT for first-line chemotherapy in mediastinal germ cell tumor patients which would seem to be in need of revision and/or further tempering based on current information. Again, mediastinal malignant seminomas are highly sensitive to standard cisplatin-based chemotherapy regimens and would likely not benefit from upfront HDCT. The evidence to currently support SDCT as the first-line chemotherapy of choice for malignant mediastinal non-seminomas include a prospective randomized clinical trial for poor-risk germ cell patients showing no benefit to HDCT. (Reference 32)

Reply 2: We modified the text according to your comment.

Changes in the text: see lines 273-276 “HDCT – to date - should not be considered as an alternative to SDCT as first-line therapeutic approach in MGCT patients, mainly because MGCTs are highly sensitive to standard cisplatin-based chemotherapy regimens and the abovementioned studies did not show a clear benefit when upfront HDCT is adopted in this specific subset of patients”.

Comment 3: Malignant mediastinal non-seminomas have a propensity to undergo somatic transformation into non-germ cell cancers which are typically chemorefractory and only cured by surgery when appropriate and likely contributed to these findings.

Reply 3: Thank you for this observation; we added a period to the text in the introductive paragraph.
Changes in the text: see lines 67-70 “Moreover, nonseminomatous MGCTs could undergo transformation into non-germ cell tumors (i.e., sarcomatous histotype), which furtherly support the surgical approach - whenever feasible - in order to avoid metastatic spread of these aggressive tumors”.

Comment 4: Finally, surgical “salvage” of operable patients with persistently elevated serum markers (indicative of persistent non-seminomatous germ cell cancer) after SDCT has a low but seemingly better chance of cure as compared to second-line HDCT therapy. (Reference 7).

Reply 4: Thank you for this observation; we added a new reference (Radaideh et al Ann Oncol 2010).
Changes in the text: see lines 65-67 “it should be mentioned also that the outcome following resection for patients with primary nonseminomatous MGCTs could be good despite the presence of rising serum tumor markers (STMs)”.

Comment 5: At our institution, HDCT is however a consideration as second-line chemotherapy in inoperable patients with persistent non-seminomatous germ cell cancer after first-line SDCT or systemic non-seminomatous germ cell cancer relapse after SDCT and surgery, with anticipated low but possible response rates.

Reply 5: Thank you for this comment; we have emphasized this notion in the conclusions.

Changes in the text: see lines 277-279: “HDCT could be therefore consideration as second-line chemotherapy in inoperable patients with persistent non-seminomatous MGCTs after first-line SDCT or advanced non-seminomatous MGCTs relapsed after SDCT and surgery, given the possibility of response”.

Reviewer C

The authors present a review of literature for standard vs high dose chemotherapy regimens in primary mediastinal germ cell tumors. This is a poorly studied subject traditionally, and this narrative describing the various studies and trials to date will add to literature. In general, the review is comprehensive and well discussed.

Comment 1: Clarify meaning of line 96 "cannot make less of cisplatin"

Reply 1: We hope to have clarified this concept by modifying the period in the text

Changes in the text: see line 103: “SDCT cannot make less ofregimens have cisplatin as their main drug cisplatin, despite short- and long-term toxicities associated with this drug”

Comment 2: Clarify meaning of line 233 "non-less relevant"

Reply 2: Thank you for this observation; we clarified this point by adding a period.

Changes in the text: see lines 244-246: “it seems to be a noless relevant problem in MGCTs patients: in fact, in these patients, cardiac and pulmonary functions, which are already impaired by the tumour, could be undermined by chemotherapy-induced toxicities”.

Comment 3: Conclusions: would be careful in discussing the use of first line HDCT in primary mediastinal germ cell tumors; while there are some small

studies describing this, certainly this would not be standard of care and would not be recommended outside of a clinical trial. In paragraph 2, would suggest softening language from "seems to be a reasonable alternative" to describe instead that it is an approach that has been minimally studied and further prospective trials are needed to determine the proper patient selection etc.

Reply 3: We modified the text according to your comment

Changes in the text: see lines 273-276 “HDCT – to date - should not be considered as an alternative to SDCT as first-line therapeutic approach in MGCT patients, mainly because MGCTs are highly sensitive to standard cisplatin-based chemotherapy regimens and the abovementioned studies did not show a clear benefit when upfront HDCT is adopted in this specific subset of patients”