Peer Review File

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Reviewer A

This is a manuscript of narrative review of induction or adjuvant systemic treatment in mesothelioma. The manuscript is well-written and contains updated information to readers, physicians, or caregivers in the area. The reviewer points out a few critiques.

1) Line 103; EPP is not abbreviated at the first appearance.
Response: Change made

2) Line 117; 'This presents three major therapeutic variables……' It is unclear what 'This' means.
Response: Wording changed to clarify**.**

3) Line 132;'this is probably the most relevant outcome to consider' It is unclear what 'this' means.
Response: Sentence clarified

Reviewer B

I have no major comments.
Minor comments:

1. Therefore, multimodality therapy employing systemic therapies before or after resection, usually with radiotherapy as well
> Radiotherapy in MPM is complex, in particular after pleurectomy/decortication, which is more and more becoming the standard of care, and should therefore be limited to centers of excellence (ASOC 2018 guideline).
> In SAKK 17/04 of 151 patients included, only 54 were finally randomized between radiotherapy and no radiotherapy. Of the 27 in the radiotherapy group, 25 completed the trial. Therefore, radiotherapy is not an option for many patients.

RESPONSE: The following sentence has been added: "Therefore, at this time, post-operative radiotherapy is usually neither feasible nor effective in the post-operative setting." (lines 199-200)

2. The addition of the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab to platinum/pemetrexed resulted in an improvement in all outcomes
> The control group in this MAPS trial also performed exceptionally well, which may suggest that the patient population was highly selected, and bevacizumab may not be a good option in 'ordinary' patients given its toxicity. Hence, it was not adopted in many countries outside of France.
RESPONSE: The following line has been added: 'Of note, the control group performed

exceptionally well and it is likely that the overall study population was highly selected and not representative of the typical mesothelioma patient." (lines 72-4)

3. In contrast, a phase III study (n = 713) of the anti-CTLA-4 agent ipilumumab and anti-PD-1 drug nivolumab demonstrated substantial benefit in terms of overall survival (18.1 vs. 14.1 months, HR = 0.74)) vs. chemotherapy (platinum/pemetrexed). PFS was similar but the duration of response for immunotherapy was substantially longer (11.0 vs. 6.7 months) ( ). Remarkably, this benefit accrued to both epithelioid and non-epithelioid subtypes
> I do not agree with this. The CM 743 trial clearly showed a benefit of nivolumab/ipilimumab in the non-epithelioid histology (and in all histologies combined), but the HR for epithelioid histology was 0.86 (CI 0.69-1.08), therefore clear superiority of N/I compared to chemotherapy is questionable.
RESPONSE: The sentence has been rephrased to clarify that the greatest degree of benefit was seen in non-epithelioid disease. (lines 90-4)

4. Complete pathologic response, when reported, is usually a marker of good prognosis.
> This is indeed often not reported, but it was reported in a number of multimodality trials/series and is usually 0 to <5% (0, 1 or 2 patients).
RESPONSE: Agree with the reviewer. The following sentence had the words, "such responses are infrequent.." added. (lines 134-5)

5. Induction therapy allows for assessment of the actual responsiveness of the tumor as well as for the ability to obtain substantial tissue for further evaluation.
> I do not understand this. Why does induction therapy lead to the ability to obtain tissue and adjuvant therapy does not? Tissue usually is obtained at diagnosis and again at surgery?
RESPONSE: By definition, adjuvant therapy is done after surgery. Therefore, tissue cannot be obtained.

> An advantage of induction therapy not mentioned here may be the presence of tumor tissue ante surgery making immunotherapy more effective (although usually tumor tissue will remain after surgery, unlike after resection of NSCLC).
RESPONSE: True, but these are usually positive margins, not gross tissue. In any event, it would require addition biopsy with no therapeutic intent.

6. Despite a number of trials, there is an absence of clear data supporting multimodality therapy in mesothelioma patients who are surgical candidates. No randomized trial has been performed.
> It is indeed true that evidence comes from surgical series and single-arm trials, but the MARS trial in the UK randomized between surgery (EPP) and no surgery. This trial did not show a benefit of surgery, although there are a number of criticisms, but was a randomized trial.
> I note this trial is reported on further on.
> ASCO 2018 guideline: Since surgical cytoreduction is not expected to yield an R0 resection, it is strongly recommended that multimodality therapy with chemotherapy and/or radiation therapy should be administered (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Response: This is stated in the conclusion, with the NCCN cited. ASCO guideline cited. (lines 264-5)

7. An analysis of the National Cancer Data Base (n= 1949) as well as the Duke University database (n = 257) in 2020 failed to demonstrate any benefit from induction therapy ( ). In fact it reached the opposite conclusion, demonstrating that induction therapy actually increased post-resection mortality (HR =1.29 for the NCDB data, HR = 1.62, for propensity matched data).
> As this was not a randomized analysis and the immediate surgery group underwent EPP considerably more often, this results might be biased by the choice of surgery (EPP in fitter patients, P/D as a more palliative approach or in patients not fit enough for EPP as used to be the case in the past). Induction patients also had lower hemoglobin and platelets, which may be a surrogate for worse performance.
RESPONSE: The NCDB/Duke study is noted to be retrospective. The data were propensity matched, which should adjust for the known factors.

8. Surgery for malignant pleural mesothelioma after radiotherapy (SMART): final results from a single-centre, phase 2 trial.
> Perhaps this recent study could be considered relevant for the manuscript?
RESPONSE: The SMART trial was an evaluation of induction radiotherapy, not systemic treatment. It is not relevant to the review.

9. Table 1: Prospective studies using induction platinum/pemetrexed for pleural mesothelioma
> At least the EORTC 08031 trial (Van Schil et al.) is missing in this table: N=58, 3 cycles cis/pem, EPP, 54 Gy.
RESPONSE: Agree. EORTC trial added to text, references and discussion.

10. Table 2: Ongoing studies of immunotherapy as neoadjuvant/adjuvant therapy
NCT 04177953: study will also apply maintenance nivolumab
NCT 02592551: started in 2016, not yet recruiting according to clinicaltrials.gov. Current status?
NCT 03760575: is also going to experiment with the surgical procedure. Interpretation of findings?
NCT 03228537: also not recruiting. Current status?
RESPONSE: The table represents the listings in CTC.gov. No information re: status of trials etc.

Reviewer C

Thank you for the opportunity to review this narrative review titled "Role of induction and adjuvant systemic therapy in mesothelioma".

The review is well written with detail account of the current status of neoadjuvant/adjuvant therapy in resectable mesothelioma and the highly variable trial design, more like flaws, that make interpretation of the results difficult.

There are a few comments that may need to be added into the manuscript.

1. On Page 4, the prognostic factors from CALGB was mentioned. It will be inclusive if the EORTC prognostic score can be added (Curran et al. JCO 1998;16:145-152).

RESPONSE: Added discussion and reference to EORTC paper. (lines 104-6)

2. On Page 6, a neoadjuvant trial of chemotherapy and radiation followed by EPP by the EOTRC was published in Eur J Resp 2010;36:1362-9, which deemed the approached not feasible should be added. This will help to strengthen your statement that neoadjuvant approached may not be feasible.

RESPONSE: Agree with the reviewer. EORTC trial added to text and table 1 as well as references. (lines 186-101, Table 1)