Peer Review File

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Reviewer comments

The authors present a retrospective study in a population of NSCLC patients, examining the ABCP regime - IO + VEGFRi + plat-based backbone chemotherapy in patients with NSCLC and aims to examine the relationship between malignant pleural effusions (MPE) in this population.

Historically regarded as a negative prognostic marker, the authors aim to investigate MPE in the context of the recent paradigm shift in NSCLC – IO + plat-based backbone chemotherapy. Previous studies have suggested that PE is associated with worse immunotherapy outcomes in NSCLC treated with ICI, including in patients with ≥50 % PD-L1 tumors and that in these patients, combination strategies should be explored.

The authors of this manuscript suggest that given the similar outcome data, ABCP may be an optimal regimen for patients with NSCLC with MPE.
Given the frequency of MPE, and the complexities in its management, even though this is a retrospective study with small numbers, it could be considered for publication if the manuscript can be amended significantly. It is well written. However there are many issues that should be addressed to allow for publication.

[Response to the reviewer]
We wish to express our appreciation to the reviewer. The comments have helped us significantly improve the paper. Our responses to the reviewer's comments are as follows:

Main points :

Inclusion
'Retrospectively enrolled' phrasing is misleading. This is a retrospective study, where 46 patients enrolled, 17 and 29 were included in the non-MPE and MPE, and retrospectively their course of therapy was examined
how the patients were selected and examined retrospectively is not explicitly stated
- the criteria for inclusion for the study in general is unclear is unclear
ie How were the patients identified and selected over the 4 year period?

Reply 1: Thank you for your valuable feedback. We retrospectively reviewed consecutive patients with advanced non-squamous NSCLC who started treatment with ABCP at our institute between January 2019 and September 2023. This is the inclusion criteria and it is simple. In the Abstract, 'retrospectively enrolled' phrasing is certainly inappropriate as you point out. We changed 'retrospectively enrolled' to 'retrospectively analyzed' (see page 3, line 43).

Changes in the text: We retrospectively analyzed consecutive patients with advanced non-squamous NSCLC who received treatment with ABCP (January 2019–September 2023).

MPE definition
'For some patients, the volume of pleural fluid was low'
- Would be useful to include more details about the pt population in terms of specifics
- How much fluid is present is obviously impactful
- Is this a well-matched group
- cytological analysis was not mandatory for the diagnosis of MPE – previous studies have included that MPE had to be cytologically proven or for e.g., radiologically and clinically relevant with no cytological proof
- it is unclear from the manuscript how MPE was defined – this needs to be clarified
- previous groups have suggested >2 metastatic sites, may be impactful -if these data are available would be useful to include
How were the patients identified and selected over the 4-year period?

Reply 2: Thank you for your insightful comments. While the primary basis for diagnosing MPE is the detection of malignant cells in pleural fluid cytology, it is not uncommon for cancer cells to be absent. Therefore, clinical and radiological factors are often considered in a comprehensive diagnosis of MPE. Diagnostic criteria for MPE can vary across studies. In this study, the measurement of pleural effusion volume in individual patients has not been performed. In this study, in patients where cancer cells were not detected in pleural fluid cytology, a diagnosis of MPE was made based on the presence of exudative pleural fluid or pleural nodules and nodular pleural thickening on a CT scan. We added this information in the Method section and modified the original text (see pages 7-8, lines 110-112).

Changes in the text: Patients who exhibited positive pleural fluid cytology results, exudative pleural effusion, or presented with pleural nodules and nodular pleural thickening along with pleural effusion on a computed tomography scan were diagnosed with MPE.

Control rate
The control rate for MPE was not defined - it is introduced as a result of importance, but never defined per se in Methods, even though in the discussion section, it is suggested that the definition of MPE control rate has varied between studies; this should be clarified

Reply 3: Thank you for your insightful comments. In this study, MPE control rate was defined as the percentage of patients without an unequivocal increase in MPE for 8 weeks after the initiation of treatment with ABCP (1, 2). The term "unequivocal increase" corresponds to the RECIST guideline's definition of progressive disease (PD). However, in this retrospective study, not all patients underwent CT up to 8 weeks after starting ABCP. In such cases, we allowed evaluation using chest X-ray to determine MPE control. We added the definition of unequivocal increase in MPE in the Method section (see page 8, lines 123-124).

1. Noro R, Kobayashi K, Usuki J, et al. Bevacizumab plus chemotherapy in nonsquamous non-small cell lung cancer patients with malignant pleural effusion uncontrolled by tube drainage or pleurodesis: A phase II study North East Japan Study group trial NEJ013B. Thoracic cancer. 2020;11(7):1876-84.
2. Kitamura K, Kubota K, Ando M, et al. Bevacizumab plus chemotherapy for advanced non-squamous non-small-cell lung cancer with malignant pleural effusion. Cancer chemotherapy and pharmacology. 2013;71(2):457-61.

Changes in the text: Unequivocal increase in MPE was defined as equivalent to progressive disease in RECIST (version 1.1).

Toxicity for each group is incomplete
Toxicity for the ABCP regime in the MPE group is presented in Table 4- similar data for non-MPE group should be included for completeness
?are there not data for thromboembolic events, which are a frequent clinical AE with these therapies?
Concusion/ Discussion statement the claim that the toxicity of this therapy in patients with MPE was acceptable – is yet to be demonstrated from the manuscript in its current state
ORR clearly favours the non-MPE group, though not reaching statistical significance

Reply 4: Thank you for your insightful comments. No thromboembolic events were observed. In this study, we focus on the toxicity in patients with MPE.

However, as you point out, we should show the toxicity profile in patients with non-MPE. The toxicity profile in patients with non-MPE was generally similar to that in patients with MPE. We added this information in the Discussion section and made supplemental table 1 (see page 17, lines 280-281). Furthermore, since AEs in patients with non-MPE were not mentioned in the Abstract, we have revised the content in the Conclusion (see page 4, lines 56-57). Finally, during this revision process, we also discovered a mistake in the Conclusions section. We inserted "non-squamous" in the last sentence (see page 18, line 296).

Changes in the text (page 17, lines 280-281): The toxicity profile in the non-MPE group was generally similar to that in the MPE group (*Supplemental Table1*).
Changes in the text (page 4, lines 56-57): The ABCP regimen may be a promising treatment option for non-squamous NSCLC patients with MPE.
Changes in the text (page 18, lines 296-297): Hence, the ABCP regimen may be a promising treatment option for non-squamous NSCLC patients with MPE.