Peer Review File

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Reviewer A

The authors conducted a retrospective study of amrubicin therapy after chemoimmunotherapy in patients with advanced small-cell lung cancer. The overall response rate was 47%, the median progression-free survival time was 3.8 months, and the overall survival time was 10 months.
There are several minor comments, as below.

Comment 1:
Page 4, line 15: What is the "local therapy"? Does it mean surgical resection or thoracic radiotherapy? Please clarify the local therapy.
Reply 1:
Thank you for the valuable comment. No patients underwent surgery, and 5 patients relapsed after radiotherapy and chemoradiotherapy. The description has been changed from "local therapy" to "radiotherapy" and "chemoradiotherapy" (Page 7, lines 11-14, and Table 1)

Comment 2:
Page 4, line 24: Five patients stopped AMR due to adverse events. According to the safety section, one patient discontinued AMR due to ILD, and another patient due to malaise. Please clarify the adverse events in the remaining 3 patients.
Reply 2:
Thank you for the valuable comment. Our apologies, 2 patients stopped AMR due to AEs, not 5 patients. Correctly, 2 patients (7%) discontinued due to adverse events, 2 patients (7%) discontinued AMR at the patients' request, and the remaining one patient (3%) was still on treatment (Page 3, line 15 and Page 7, lines 21-24).

Comment 3:
Page 5, line 35: PEG-G-CSF was used in 13 patients, of which 2 patients (15%) developed FN after the use of PEG-G-CSF. These data should be described in the Results at first, not in the Discussion.
Reply 3:
We agree with the reviewer's advice. These data were described in the Results (Page 8, lines 20-21)

Comment 4:

Page 5, line 42: One patient developed grade 2 ILD after AMR therapy. This information (grade of ILD) should be also described in the Results at first, not in the Discussion.

Reply 4:

Thank you for your advice. In the “Results” section, we stated that ILD occurred in one case (page 8, line 19).

Comment 5:

Figure 1 and 2: Please indicate the censored cases as tick-marks on the Kaplan-Meier curves.

Reply 5:

We would like to thank the reviewer for this advice. We have edited the figures 1 and 2 to indicate the censored cases.

Reviewer B

This original article entitled "Efficacy and safety of amrubicin therapy after chemoimmunotherapy in small cell lung cancer patients (#62513)" reported the efficacy of AMR for ED-SCLC after chemoimmunotherapy. The authors concluded the survival benefit and no significant difference was seen between sensitive and refractory relapse as well as Safety was satisfied.

major comment.

A. strength

multi-center

Reply A:

Thank you for the valuable comment. A total of eight institutions participated in this study. We consider the multicenter nature of this study to be one of its strengths.

B. weakness

1. Too small sample size

Reply 1:

The limitation of the current study was relatively small sample size. Future study is warranted to confirm the findings in this study. We stated the limitation of this study in the “Discussion” section (Page 11, lines 11-13).

2. Amurubicin is the local drug in Japan, therefore, this issue should be shared in a local journal, not an international journal.

Reply 2:

Thank you for your comment. Although amrubicin cannot be used worldwide, it is available in Japan as well as in China and other countries, therefore we submitted this manuscript to an international journal. We believe that the data provided in this manuscript is useful for readers of Translational Lung Cancer Research. We state this limitation on page 11, line 13.

3. Treatment discontinuation was 17%. It was not always enough in the relapse SCLC.

Reply 3:

Thank you for the valuable comment. Our apologies, 2 patients (7%) stopped AMR due to AEs, not 5 patients (17%). Correctly, 2 patients (7%) discontinued due to adverse events, 2 patients (7%) discontinued at the patients' request, and the remaining one patient (3%) was still on treatment (Page 3, line 15 and Page 7, lines 21-24).

minor comment

1. Chemoimmunotherapy is not "dramatically" improved survival.

Reply 1:

We agree with the reviewer's comment. We have revised the Abstract according to the reviewer's advice (Page 3, lines 1-3)

2. Introduction. The description SOC for ED-SCLC has not matched the US and Euro guidelines in the introduction section. Specify which guideline is listed or revise them.

Reply 2:

Thank you for the valuable comment. We have revised the Introduction section according to the reviewer's comment (Page 4, lines 4-8).

3. Method; Clarify how to have collected data and who has collected data or cleaned data.

Reply 3:

We would like to thank for this reviewer's comment. We collected data using the case report forms. The data cleaning was carried out by the clinical trial office of the Niigata Lung Cancer Treatment Group ant authors. We have revised the Material and Methods section to include these information (Page 6, lines 11-13).

Reviewer C

The authors retrospectively analyzed safety and efficacy of amrubicin (AMR) in SCLC patients who were previously treated with etoposide, carboplatin, and atezolizumab, and the results were quite similar to those previously reported in

SCLC patients who were treated with chemotherapy alone. Regrettably, the authors failed to provide new insight in the treatment of SCLC in this settings, and similar results have been reported in NSCLC. I should say that this paper is short of the level needed to be accepted for the publication in TLCR.

Reply:
We thank the reviewer for the advice. Currently, the standard treatment for recurrent small cell lung cancer after chemoimmunotherapy is empirical treatment due to a lack of evidence. Therefore, we believe that this study, which confirmed both the efficacy and safety of amrubicin therapy after chemoimmunotherapy, can provide useful information to the readers of Translational Lung Cancer Research.

Reviewer D

In this manuscript (TLCR-22-225), Kushiro, at.al, demonstrate a retrospective study which shows the effect of Amrubicin (AMR) for the patients with small cell lung cancer (SCLC) as the second line treatment after chemoimmunotherapy. They show that a certain therapeutic effect of AMR (ORR was 47%, median PFS was 3.8 months, and the median OS was 10 months) with manageable toxicities. There is no significant difference between the sensitive and refractory groups about the effect of AMR.
Since there is few information about the effective second line treatment after chemoimmunotherapy for the patient with SCLC, the reviewer thinks that this is well-performed, clinically important study although this is a retrospective and small cohort study.

The following concerns need to be addressed to elevate the findings of the manuscript.

Minor Comments
#1
In this study, ten patients (33%) were treated with AMR at a dose of 40 mg/m2, 12 patients (40%) received 35 mg/m2, and 8 patients (27%) received 30 mg/m2.
Because the standard dose of AMR is 40 mg/m2, the above dosages might have effects on the result. The reviewer recommends to address about it in the limitations of the study.
Reply #1:
We are thankful for the reviewer's valuable advice. We added a sentence as advised (Page 11, lines 18-20)

#2

As the authors mentioned, this is a retrospective observational study and that the number of cases is relatively small. Reviewer recommends to add the sentence of 'the prospective studies will be required to further evaluate the effect of AMR or other cytotoxic agents after chemoimmunotherapy for the patients with SCLC in the future.'

Reply #2:

We agree with the reviewer's comment. We have revised the limitation according to the reviewer's advice (Page 11, lines 11-13).

#3

In the abstract, the term 'extended disease' should be 'extensive disease'. Or term of 'extensive-stage (ES)' is the global standard although the term of 'extensive disease (ED)' is commonly used in Japan. Please be consistent with the term through the manuscript in either representation.

Reply #3:

Thank you for pointing out the error. We have revised the Abstract (Page 3, line 2)