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Reviewer A

Authors reported that a Clinical impact of amrubicin monotherapy in patients with relapsed small-cell 2 lung cancer by a multicenter retrospective study. This is very interesting report, but I would like to mention some reviewer's comments.

Comment A-1: Authors showed that in the multivariate analysis for PFS (Fig.4b), “poor ECOG PS at AMR initiation” was an independent predictor of PFS, however, “Use of platinum plus etoposide at the first-line treatment” was not an independent predictor of PFS. Meanwhile, in the Abstract section, authors concluded that different types of topoisomerase inhibitors could affect the efficacy of amrubicin monotherapy in the second-line treatment of patients with relapsed extensive-stage small-cell lung cancer. I wonder whether the abovementioned is appropriate.

Reply A-1: We appreciate the reviewer for the insightful comments. Multivariate and propensity score matching analyses were done for the “75 years old” cut-off, based on your comment A2 (below). The multivariate analysis results demonstrated that, “poor ECOG PS at AMR initiation” and “Use of platinum plus etoposide at the first-line treatment” were independent prognostic factors of PFS with amrubicin monotherapy, consistent with those of propensity score matching analysis. We have revised the texts in the results section and Tables 4A and B.

Changes in the text:

(Pages 13-14, lines 246-253.) Thus, the multivariate analysis demonstrated that platinum plus etoposide at the first-line treatment and poor PS at amrubicin initiation were independent prognostic factors for prolonged PFS following amrubicin monotherapy (Table 4B).

Comment A-2: In the past, the age of SCLC patients has been divided at 70 years old, but I think it is more realistic to divide the age at 75 years old instead of 70 years old in the Japanese lung cancer treatment. Authors should evaluate PFS according to the age based on "75 years old".

Reply A-2: As the reviewer recommended, we additionally evaluated PFS according to the age based on ‘75 years old.’ In this additional analysis, the trend of some values, including PFS, was similar to the ‘70-year-old’ cut-off, but there were some changes, including multivariate analysis. Therefore, we revised the results to reflect the new outcomes in Tables 1, 3, 4A and B, Figure 3, and Supplementary Figure 1.

Changes in the text:

(Page 13, lines 239-242)

A significant difference in the PFS following amrubicin monotherapy was observed between the irinotecan and etoposide groups in the propensity score matching analysis (median: 3.4 vs. 2.1 months, p = 0.03; Figure 3).

(Pages 13-14, lines 246-255)

Thus, the multivariate analysis demonstrated that platinum plus etoposide at the first-line treatment and poor PS at amrubicin initiation were independent prognostic factors for prolonged PFS following amrubicin monotherapy (Table 4B). In this study, PFS with amrubicin was evaluated in the aging of patients ≥ 70 and those ≥ 75 years. The results of ≥ 70 years old patients were similar to those of ≥ 75 years, compared with the younger patients (Supplementary Figure 1).

Reviewer B

It is a meaningful and interesting topic.

The authors report that different types of topoisomerase inhibitors could affect the efficacy of amrubicin monotherapy in the second-line treatment of patients with relapsed extensive-stage small-cell lung cancer. Although the data are clinically important, we believe that some revisions are necessary.

Major points

Comment B-1: In practice, when small cell lung cancer relapse, the subsequent treatment option is considered based on whether the case is “sensitive” or “refractory”. If both sensitive and refractory cases are included in this study, it would be useful for the reader to take them into account in the analysis.

Reply B-1: We appreciate the meaningful comments. As the reviewer recommended, the analysis based on the difference between ‘sensitive’ and ‘refractory’ relapse patients within 90 days, and the impact of the first-line treatment on the clinical outcomes of amrubicin monotherapy were evaluated. The PFS following amrubicin monotherapy was significantly longer in sensitive than in refractory-relapsed patients ($p < 0.001$) in the etoposide group. In contrast, there was no significant difference in the PFS following amrubicin monotherapy between sensitive and refractory-relapsed patients ($p = 0.19$) in the irinotecan group, shown in Figures 6A and B, respectively.

Changes in the text:

(Page 10, lines 161-163.) **Methods (Patients)**

The relapse-free interval of the first-line treatment was also extracted and classified into sensitive or refractory relapse based on whether the period exceeded 90 days.

(Page 15, lines 284-294.) **Correlation between the efficacies following first-line treatment and amrubicin monotherapy**

The impact of the recurrence on the clinical outcomes of amrubicin monotherapy was evaluated by classifying both the irinotecan and etoposide groups into two groups based on the period from the last administration of the first-line treatment to recurrence. The PFS following amrubicin monotherapy was significantly longer in sensitive-relapsed patients than in refractory-relapsed patients (4.1 vs. 1.8 months, Peto-Peto–Wilcoxon test, $p < 0.001$) in the etoposide group (Figure 6A). In contrast, no significant difference in the PFS following amrubicin monotherapy between sensitive-relapsed and refractory-relapsed patients (4.3 vs. 3.0 months, Peto-Peto–Wilcoxon test, $p = 0.19$) in the irinotecan group (Figure 6B).

Comment B-2: The term "PFS" is used in multiple ways and is difficult to understand. The term PFS is used for various starting points, and the PFS used for different points should be more clearly indicated.

Reply B-2: As the reviewer pointed out, we clarified the definition of each PFS in the material and methods section and revised the indications of PFS, such as Correlation between the PFS of first-line treatment and PFS of amrubicin monotherapy in the second-line setting.

Changes in the text:

(Page 11, lines 192-195.) **Methods (Statistics)**

PFS of amrubicin was defined as the time from the initiation of amrubicin to disease progression, or death from any cause. PFS of the first-line treatment was defined as the time from the initiation of the first-line treatment to disease progression.

Comment B-3: In this study, only PFS was analyzed and OS was not analyzed. PFS or TTF (treatment to failure) is appropriate when evaluating the efficacy of a drug regimen, but its impact on OS is not always consistent with the efficacy of the regimen. I recommend an additional analysis of OS, which can be evaluated absolutely in terms of mortality events.

Reply B-3: As the reviewer recommended, we have added the OS analysis to Figures 2C and 2D. There was no significant difference in OS between irinotecan- and ETP-containing regimens.

Changes in the text:

(Page 10, lines 146-147) **Methods (Patients)**

Overall survival (OS) was defined as the time from the first administration of platinum-based chemotherapy until any cause of death.

(Pages 15, lines 296-298) ***Overall survival analysis***

At the date of data cut-off, the median follow-up was 13.6 months. No significant differences were observed between the OS of the irinotecan and etoposide groups (14.0 vs. 13.6 months, Peto-Peto–Wilcoxon test, $p = 0.35$) (Figures 2C and D).

Comment B-4: The study evaluated efficacy only and did not provide important safety data. It would be useful for readers to know whether there were differences in adverse events between irinotecan and etoposide group.

Reply B-4: As the reviewer pointed out, we mentioned that adverse events based on CTCAE version 5.0 were extracted from medical records and the safety data of amrubicin monotherapy in irinotecan- and etoposide-containing groups were added to the text and Supplementary Table 1.

Changes in the text:

(Page 10, lines 159-160.) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

(Page 16, lines 315-325.) ***Safety***

Fifty patients in the irinotecan group and 241 in the etoposide group were evaluated for the safety of amrubicin monotherapy. Grade ≥ 3 CTCAEs were observed in 78% and 64.3% of patients in the irinotecan and etoposide groups, respectively ($p = 0.07$). Grade ≥ 3 neutropenia was more frequently reported in the irinotecan group than in the etoposide group (78% vs. 57.9%, $p = 0.01$). However, the incidence of febrile neutropenia was not of significance ($p = 1$). Grade ≥ 3 pneumonitis were observed in both groups (4% vs. 7%, $p = 0.75$). Discontinuation due to adverse events caused by pneumonitis and neutropenia occurred in both groups (10.5% vs. 13%, $p = 0.82$) and treatment-related deaths were observed in 6 patients (2.5 %) of the etoposide group (Supplementary Table 1).

Comment B-5: At present, the standard treatment for extensive disease small cell lung cancer is cytotoxic anticancer drugs plus immune checkpoint inhibitors, but regimens that include irinotecan cannot be used in combination with immune checkpoint inhibitors. It is desirable to mention under what situations irinotecan should be used.

Reply B-5: We have mentioned that irinotecan-containing chemotherapy could be a better option in the discussion section, for example, ineligible patients for immune

checkpoint inhibitors, such as autoimmune diseases who have a high risk of severe immune-related adverse events.

Changes in the text:

(Page 18, lines 370-373) In contrast, platinum plus irinotecan treatment still could be a better option for ineligible patients for immune checkpoint inhibitors, such as autoimmune diseases with a high-risk of severe immune-related adverse events.

Minor points

Comment B-6: Survival time is shown in days, but most of the recent studies show survival time in months, thus it is recommended to convert it to months if possible to simplify comparison with other studies.

Reply B-6: We have converted days to months in the revised manuscript.

Comment B-7: Figure 6 may be included only in the text because the number of cases in the atezolizumab group is small and has little impact. Since there are many figures, figure 6 could be deleted or made into Supplement Figures.

Reply B-7: As the reviewer suggested, we have made Figure 6 into Supplementary Figure 2.