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Treatments for relapsed-refractory diffuse large B-cell lymphoma: comparison of overall survival outcomes observed with four novel agents

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Abstract. – OBJECTIVE: Tafasitamab, loncastuximab, tesirine, polatuzumab, and selinexor have been proposed for the treatment of relapsed/refractory B-cell lymphomas. We studied the patterns of overall survival (OS) for these four agents.

PATIENTS AND METHODS: We reconstructed patient-level data from the published Kaplan-Meier OS graphs. For this purpose, we used an artificial intelligence technique (the Shiny method). Reconstructed survival curves were then subjected to standard statistics to perform between-treatment comparisons, and hazard ratios (HRs) and 95% confidence intervals (CI) were estimated.

RESULTS: Using tafasitamab plus lenalidomide as a common comparator, our analysis of OS yielded the following results: a) Polatuzumab vedotin vs. tafasitamab + lenalidomide: HR=1.60 (95%CI, 0.94-2.74, *p*=0.0831); b) Selinexor *vs.* tafasitamab + lenalidomide: HR=2.28 (95%CI, 1.54-3.38, *p*<0.001); c) Loncastuximab tesirine *vs.* tafasitamab + lenalidomide: HR=2.35 (95%CI, 1.55-3.56, *p*<0.001). All three values favored tafasitamab + lenalidomide.

CONCLUSIONS: These comparative OS results represent the original findings. Although these comparisons were indirect, our analysis offered a useful synthesis of the outcomes reported thus far for these four treatments.

Key Words:
Relapsed-refractory non-Hodgkin lymphoma, Overall survival, Tafasitamab, Lenalidomide, Loncastuximab tesirine, Polatuzumab vedotin, Selinexor.

Introduction

Recent reviews[1,2] have examined novel treatments for relapsed-refractory diffuse large B-cell lymphoma, including CAR T-cell products and novel pharmacological agents. With regard to CAR-T cell products, numerous reports have been published, and emphasis has been placed on studying overall survival (OS), including long-term extrapolations. For example, in February 2022, Roschewski et al[3] presented an updated comparative analysis of the current literature on CAR-T products. In contrast, regarding non-CAR-T agents, an updated overview of novel treatments has not been published recently. Therefore, conducting such an analysis would be worthwhile.

Tafasitamab, loncastuximab tesirine, polatuzumab, and selinexor have been recently proposed to expand the armamentarium for this specific disease condition. A review by Nuvvula et al[2] examined the response rates observed with these four therapies, but no systematic analysis of overall survival (OS) was presented.

As OS is the most critical outcome in this disease condition, we conducted an analysis aimed at comparing the OS outcomes reported for these four agents. As clinical material for our analysis, we selected pivotal trials published for these agents[4-7]. Regarding the methods of our analysis, we applied a new technique (Shiny method[8]) that employs an artificial-intelligence approach to examine the Kaplan-Meier curves and reconstruct the databases of individual patient data. The generation of pooled survival curves from reconstructed individual patient data has already been used in a number of previous studies[9-13], mostly focusing on anticancer treatments.

Patients and Methods

Study Design

The present analysis was designed to study patients with relapsed-refractory diffuse large B-cell lymphoma treated with four novel treatments (tafasitamab, loncastuximab tesirine, polatuzumab, or selinexor). The clinical material was represented by the pivotal trial published for each of these four agents. OS was the endpoint of the analysis. Our aim was to carry out indirect

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comparisons among these four treatments by applicating the Shiny method.

Statistical Analysis

For each clinical study, we examined the Kaplan-Meier graph of OS (along with the total number of enrolled patients and total number of deaths). Then, for each OS curve, we reconstructed patient-level data from the graph using the Shiny method[8]. The graph of each Kaplan-Meier curve was digitalized and converted into *x*-y data pairs using a Webplotdigitizer (Ankit Rohatgi, Pacifica, CA, USA). The Shiny package[8] was used to reconstruct the patient-level data. This combined application of the Webplodigitizer and Shiny software is well standardized[8-13].

Finally, the reconstructed survival curves for the four treatments were pooled into a single Kaplan-Meier graph, which was handled according to standard statistical analyses. Pairwise statistical comparisons were handled by determining the hazard ratio (HR) along with 95% confidence interval (CI). Medians (with 95%CI) were also determined. Statistical significance was set at $p < 0.05$. All calculations were performed using the R-platform[14]; three packages ("coxph", "survfit", and "ggsurvplot") were used.

Results

Table I illustrates the main characteristics of the four trials. After reconstructing individual patient data according to the Shiny method, we generated the Kaplan-Meier curves of OS illustrated in Figure 1.

The following median values were estimated:

a) Tafasitamab + lenalidomide (Duell et al[4]): 26.5 months (95%CI, 18.39-NR);
b) Polatuzumab vedotin (Sehn et al[6]): 12.5 months (95%CI, 9.03-not reached);
c) Loncastuximab tesirine (Caimi et al[5]): 10.2 months (95%CI, 6.97-11.6);
d) Selinexor (Kalakonda et al[7]): 10.1 months (95%CI, 6.72-14.2).

According to the medians, tafasitamab + lenalidomide ranked first, polatuzumab vedotin second, loncastuximab tesirine third, and selinexor fourth.

Regarding the indirect pairwise comparisons between these agents, tafasitamab + lenalidomide (i.e., the treatment with the best OS profile) was selected as a common comparator for the other three agents. Our pairwise comparisons yielded the following results:

a) Polatuzumab vedotin *vs.* tafasitamab + lenalidomide: HR=1.60 (95%CI, 0.94 to 2.74; p=0.0831);
b) Selinexor *vs.* tafasitamab + lenalidomide: HR=2.28 (95%CI, 1.54 to 3.38, p<0.001).

Table I. Basic information about inclusion criteria and OS outcomes from the 4 trials included in our analysis.

Trial (first author, year of publication)	Inclusion criteria	Treatment	No. of patients	No. of events
Duell et al[4], 2021	Patients with relapse or progressive disease 3 to 6 months from frontline therapy[§]	Tafasitamab + lenalidomide	80*	48*
Sehn et al[6], 2020	Patients with transplantation-ineligible relapsed/refractory diffuse large B-cell lymphoma	Polatuzumab vedotin	40	29
Caimi et al[5], 2021	Patients aged 18 years or older with relapsed or refractory disease after two or more multiagent systemic treatments, who had measurable disease and Eastern Cooperative Oncology Group performance status 0-2	Loncastuzimab tesirine	145	77
Kalakonda et al[7], 2020	Patients aged 18 years or older with pathologically confirmed diffuse large B-cell lymphoma, an Eastern Cooperative Oncology Group performance status of 2 or less, who had received 2-5 lines of previous therapies, and progressed after or were not candidates for autologous stem-cell transplantation	Selinexor	127	73

*In the original trial, the 80 patients were reported in three subgroups of 14, 32, and 34 patients; the 48 events were reported as 15+8+25 in the three subgroups, respectively.
[§]The inclusion criteria were revised while the study was ongoing (see the original paper for further details[4]).

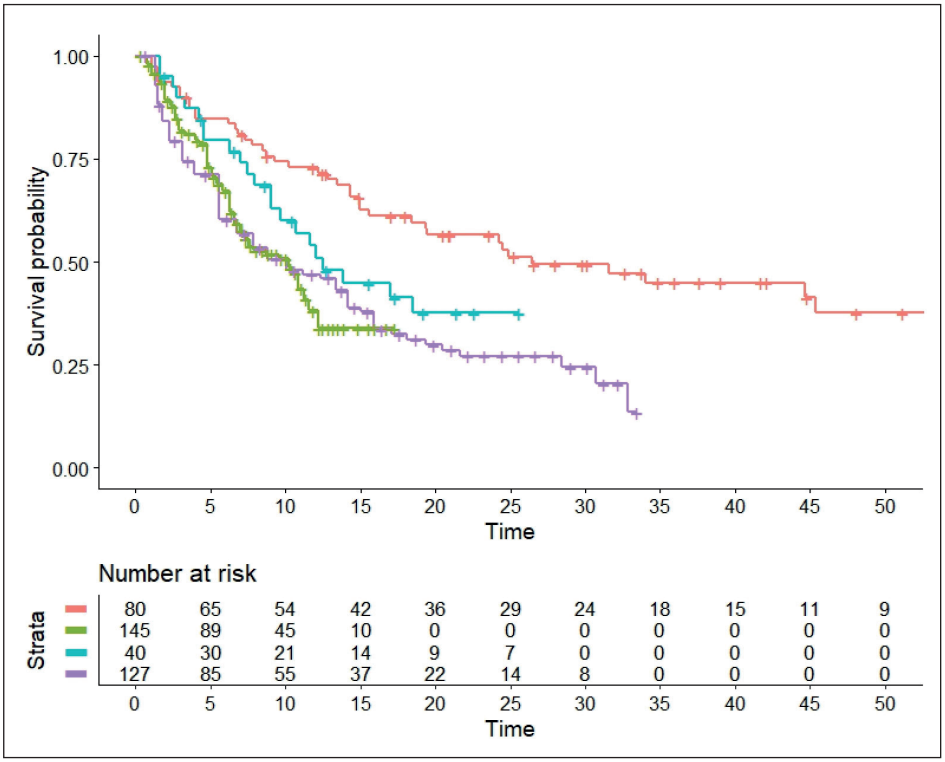

Figure 1. The 4 Kaplan-Meier curves refer to the following treatments: a) tafasitamab + lenalidomide (in red); b) loncastuximab tesirine (in green); c) polatuzumab vedotin (in light blue); d) selinexor (in purple). Endpoint, overall survival.

c) Loncastuximab tesirine *vs.* tafasitamab + lenalidomide: HR=2.35 (95%CI, 1.55 to 3.56, $p<0.001$).

These three HR values were all in favor of tafasitamab + lenalidomide.

Indirect statistical comparisons are essential for interpreting the descriptive results shown in Figure 1. As judged by the endpoint of OS, the ranking in medians was a preliminary but useful information to compare the effectiveness of these 4 agents. Thereafter, the values of HR quantified these comparisons in more depth and provided the commonly used indexes of statistical significance. Finally, regarding the other pairwise comparisons in all combinations, some differences were significant, whereas others were not (data not shown).

Overall, the basic results of our analysis were effectively summarized by a few information represented by the values of HR and by the Kaplan-Meier graphs.

Discussion

The main original finding of this study is represented by the Kaplan-Meier graph, where the overall survival pattern was reported for the four treatments (Figure 1). First, visual inspection of this graph permits ranking effectiveness across the four treatments and evaluating the clinical relevance of survival differences; thereafter, formal comparisons are generated through standard statistics that evaluate the significance of the differences.

Our results clearly favor the combination of tafasitamab and lenalidomide. Although this finding must be viewed with caution owing to the indirect nature of the comparisons, the magnitude of incremental benefit for tafasitamab + lenalidomide was remarkable, which explains the rationale for undertaking trials of direct comparison based on this combination treatment.

The differences in OS that we found might depend on intrinsic differences in effectiveness across the treatments or different characteristics of the enrolled patients. It is most likely that both factors played a role. Regarding the patient eligibility criteria, these were very similar in the four trials, but not the same; therefore, the patients' cohorts included in our analysis likely did not have the same risk or prognosis. However, the extent to which this factor contributed to the final results remains unknown.

One important advantage of the Shiny method[8] lies in its ability to evaluate the time course of survival patterns. In contrast, in a standard meta-anal-

ysis, where the survival differences are expressed through a Forest plot, no information is generated about the survival trends over time. In both cases, the HRs provide the final results, but the advantage of the Shiny method is that the Kaplan-Meier graphs convey more information than the Forest plot.

In the framework of graphs generated by the Shiny approach, further analyses can be performed to separately handle the area under the curve from time zero to the last time point in the follow-up and the area under the curve from the last time point to infinity (yielding the so-called "lifetime survival extrapolations"). Extrapolation of survival curves is frequently used to quantify OS outcomes with CAR-T products[15]. Hence, the availability of Kaplan-Meier curves for non-CAR-T agents (such as those presented in Figure 1) could be useful to carry out further indirect comparisons between CAR-T cell products and non-CAR-T agents.

The present work has the typical limitations of all analyses based on the Shiny method[12,13]. Among these, the most relevant is that these comparisons are indirect; hence, the results may be affected by differences in the original patient cohorts, as previously pointed out.

Conclusions

The experience presented herein demonstrates the feasibility of reconstructing patient-level data from survival graphs to generate survival statistics and to synthesize clinical evidence.

Regarding the analysis of these four treatments, the results of our statistical comparisons represent an original finding, which also has the advantage of a format particularly rich in evidence-based information.

Application of the Shiny method is still in its early stages. However, since an increasing number of analyses are being carried out[8-13], these analyses will hopefully more clearly identify the role that can be attributed to the Shiny method in analyzing clinical evidence. Finally, to evaluate the performance of the Shiny approach, further studies could be useful in comparing statistical results (e.g., HRs) between reconstructed and originally published datasets.

Conflict of Interests

The authors declare no conflict of interest.

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Informed Consent

Informed consent from patients was not necessary because the analysis relied on clinical material already published in previous reports.

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Data Sharing Statement

All the materials used for conducting the survival analyses are available from the authors upon request.

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