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CLINICAL TRIALS AND OBSERVATIONS

Comment on Belada et al, page 1348

A new frontier for R-CHOP: is two better than one?

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In this issue of *Blood*, Belada et al report the results of the First-MIND open-label, multicenter, randomized phase 1b study of tafasitamab added to standard rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with or without lenalidomide in newly diagnosed diffuse large B-cell lymphoma (DLBCL) in patients with International Prognostic Index (IPI) 2 to 5.[1] The authors show that the addition of tafasitamab and lenalidomide (T/L) to R-CHOP was safe with promising signals of efficacy.

Tafasitamab is a humanized monoclonal antibody targeting CD19. The combination of tafasitamab with lenalidomide showed an excellent overall response rate (ORR) of 60% in relapsed/refractory (R/R) DLBCL, and this combined regimen is currently licensed for use in patients with R/R DLBCL who are ineligible for autologous stem cell transplant.[2] Based on these promising results, the authors conducted this study to assess safety and preliminary efficacy of tafasitamab added to standard R-CHOP[3] with or without lenalidomide as first-line therapy in patients with DLBCL. From December 2019 to August 2020, 83 patients with newly diagnosed, untreated DLBCL (Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0-2, IPI 2-5) were screened, and 66 that fulfilled inclusion criteria were enrolled and randomized to receive R-CHOP + tafasitamab (arm T) or R-CHOP + tafasitamab + lenalidomide (arm T/L) for 6 cycles. The authors show that the addition of T/L to R-CHOP was safe with an acceptable increased incidence of adverse effects in comparison with a previous study with R-CHOP + lenalidomide (LR-CHOP).[4] The majority of adverse events were hematologic toxicities that were reported more frequently in T/L R-CHOP. Nonhematologic toxicities were superimposable between the 2 arms. Regarding outcome, the authors report a trend for superior efficacy of the combination T/LR-CHOP compared with LR-CHOP, in terms of ORR, duration of response, progression-free survival (PFS), and overall survival (OS). However, the number of patients was limited, and the study was not powered for efficacy end points. These results, with the limitation of the small sample size and a short follow-up, are comparable to those reported by previous studies (see table).

The attempt to improve R-CHOP results of first-line therapy in patients with DLBCL has been the focus of many studies for the last 2 decades. In the randomized phase 3 trial GOYA-BO21005, the humanized anti-CD20 obinutuzumab in addition to CHOP did not improve the outcome compared with standard R-CHOP in 1418 patients with DLBCL.[5] These results show that chemoresistance in first-line treatment was not overcome by only substituting the monoclonal antibody. Based on the advances in the understanding of the biology of DLBCL, subsequent studies focused on the different cell-of-origin (COO) profiles. The activated B-cell (ABC) or nongerminal B-cell (non-GCB) lymphomas were associated with poor outcome in series of patients treated with R-CHOP. Therefore, randomized phase 3 trials were focused on patients with non-GCB or ABC DLBCL, testing drugs targeting the ABC profile. In the Phoenix trial, the Bruton kinase inhibitor ibrutinib plus R-CHOP was compared with R-CHOP in patients with untreated non-GCB DLBCL.[6] No advantage in terms of PFS was observed, and the study did not meet the primary end point. Nevertheless, in a subgroup analysis, an advantage in the ibrutinib-R-CHOP arm was shown in patients who were young and those with overexpression of Bcl-2 and Myc. In the phase 3 double-blinded international ROBUST trial, ABC profile patients were randomized to receive R-CHOP vs LR-CHOP (with lenalidomide 15 mg, day 1-14 during each R-CHOP courses).[4] This study was also negative, with superimposable PFS and OS between the 2 arms, but a subgroup analysis suggested some benefits using LR-CHOP in high-risk patients (IPI 3-5). These results suggested that selecting patients based on COO was not a sufficient strategy to select new treatments. Recently, a phase 3 trial, the POLARIX study, tested the combination of polatuzumab-vedotin (Pola), an antibody drug conjugate that targets CD79b, with R-CHP (CHOP without vincristine) vs R-CHOP.[7] The POLARIX met the primary end point, demonstrating a marginal but significant advantage in the 2-year PFS for Pola-R-CHP compared with R-CHOP, with comparable safety profiles but no differences in OS. Based on these results, the combination Pola-R-CHP may represent a new standard as first-line treatment for some patients with DLBCL.

The First-MIND study is based on a possible synergist effect of T/L to enhance effector cell activity. For the first time 2 targeted drugs were combined with R-CHOP to try to overcome chemoresistance. One limitation of the

First-line chemoimmunotherapy combinations for newly diagnosed DLBCL

Regimen	Study phase	Number of patients	Median age (range), y	Cell of origin	ORR/CR (%)	PFS (%)	OS
TR-CHOP[1]	1b	33	64 (20-86)	All DLBCL	76/73	73 (2 year)	90 (2 year)
T/LR-CHOP[1]	1b	33	64 (20-86)	All DLBCL	82/67	77 (2 year)	94 (2 year)
R-CHOP[3]	3	202	69 (60-80)	All DLBCL	82/52	57 (2 year)	70 (2 year)
Obinutuzumab-CHOP[5]	3	704	62 (18-86)	All DLBCL	77/57	73 (2 year)	84 (2 year)
Ibrutinib-CHOP[6]	3	419	63 (19-88)	Non-GCB	89/67	70 (2 year)	85 (2 year)
LR-CHOP[4]	3	285	65 (21-82)	ABC	91/69	75 (2 year)	79 (2 year)
Pola-R-CHP[7]	3	440	65 (19-80)	All DLBCL	85/78	77 (2 year)	89 (2 year)

CR, complete response.

present study is the small number of patients in the 2 cohorts that makes difficult a proper evaluation of the differences in efficacy between the 2 arms (T or TL added to R-CHOP). However, the biological rationale of the combination T/L and the trend of superiority in the combination T/LR-CHOP compared with LR-CHOP supports the further exploration of this combination. Indeed, First-MIND represents the basis for the ongoing multicenter international phase 3 double-blinded randomized Front-MIND study in first-line high-risk DLBCL, which recently concluded enrollment and should determine whether T/LR-CHOP is superior to R-CHOP.[8] Using an anti-CD19 agent in first-line treatment could potentially hamper the efficacy of anti-CD19 chimeric antigen receptor T cell (CAR-T) in case of relapse after T/LR-CHOP.[9] The analysis of 12 tumor lymph node biopsies (4 pretafasitamab and 8 posttafasitamab) of 6 patients with R/R DLBCL enrolled in the L-MIND trial[2] showed consistent CD19 mRNA expression levels in cases exposed to tafasitamab, suggesting that CAR-T therapy after tafasitamab exposure may be possible.[10] However, data are very limited and should be confirmed in larger series.

In conclusion, the dream of finding a more effective front-line treatment in DLBCL is still alive, and several combinations are being tested. Combining 2 different compounds to standard R-CHOP, such as the present T/LR-CHOP regimen, may well be a sound strategy. Other ongoing regimens under investigation with bispecific anti-CD20xCD3 antibodies plus R-CHOP or Pola-R-CHP are on the way. All together these novel treatments represent new strategies to reach the ultimate goal of increasing the initial rate of cure for patients with intermediate or high-risk DLBCL.

Conflict-of-interest disclosure: U.V. declares participation in advisory boards for Genmab, AbbVie, Regeneron, and Gilead; and lecture honoraria for AbbVie, Incyte, Regeneron, and Roche. A.C. declares participation in advisory boards for Gilead-Sciences, Roche, Ideogen, and Takeda; and educational activities/lecture fees for AstraZeneca, Gilead Sciences, Incyte, Janssen-Cilag, Novartis, Roche, and Takeda. ■

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https://doi.org/10.1182/blood.2023021521