Until now, the standard of care for relapsed/refractory (rr) diffuse large B-cell lymphoma (DLBCL) has been salvage by second-line treatment and consolidation by autologous stem cell transplantation (ASCT) if patients are chemosensitive and in complete remission (CR) with a negative positron emission tomography (PET) scan pretransplantation. With the advent of chimaeric antigen receptor-modified T cells targeting CD19 (CAR-T19), patients with rr DLBCL after front-line therapy now have multiple treatment options that can lead to a cure. The identification of patients who should be prioritized for ASCT versus non-chemotherapy treatment is a critical issue.

In their paper, Cherng and colleagues discuss the eligibility of patients not in CR after salvage therapy for standard ASCT. These patients include partial responders (PRs) or those with stable disease (SD) who are still PET-scan-positive with a Deauville (DS) five-point score (5PS) of 4 or 5. Should these patients be excluded from the ASCT procedure considering that it is a major adverse prognostic factor resulting in eventual failure? In the multicentre prospective CORAL study of relapsed/refractory DLBCL patients evaluating the benefit of two different salvage regimens, the three-year progression-free survival (PFS) was 53% in patients who underwent ASCT. No difference was observed between the patients who achieved radiologic CR or PR immediately before ASCT. The PET scan was not part of the study, and metrics for chemosensitivity in patients with residual disease were not well known.

The reported article performed a retrospective dynamic evaluation of positive PET scans pretransplantation with variations in radiometrics among a subgroup of 92 rr DLBCL patients who received ASCT. Patients were followed in the same institution with the same standard of care and physicians. Among the 489 lymphoma patients transplanted during this period, only patients with a PET scan DS of 4 or 5 were included in this study. (i.e., 67 PR patients and 23 SD patients) Patients with progressive disease or those in CR with a DS of 2–3 were not included. PET scan metrics that
were assessed pre ASCT included a maximum standardized uptake value (SUV$_{\text{max}}$) greater than 11 in 21 patients, high total metabolic tumour volume (TMTV > 29.5 ml) in 22 patients and total lesion glycolysis (TLG > 110) in 23 patients. Patient characteristics were reported at the time of transplant (table 1 in Cherng et al.). The population was representative of that observed in rr DLBCL patients. Tumour bulk larger than 5 cm was evaluated pre ASCT and was observed in 47 patients, and early relapse (i.e., <12 months) was noted in 66 cases.

The five-year PFS and overall survival (OS) rates were 40% and 54% respectively. Here, a 5PS of 5 ($p = 0.0082$, hazard ratio (HR) 2.09), high SUV$_{\text{max}}$ ($p = 0.0015$, HR 2.48), TMTV ($p = 0.035$, HR 1.83), and TLG ($p = 0.0036$, HR 2.27) were associated with inferior PFS. A 5PS of 5 ($p = 0.030$, HR 1.98) and high SUV$_{\text{max}}$ ($p = 0.0025$, HR 2.55) were associated with inferior OS. PET-derived parameters may help prognosticate outcomes after ASCT in patients with rr DLBCL with residual disease PET and after salvage therapy. The main parameters predicting OS and PFS were high SUV$_{\text{max}}$ before transplant and a 5PS of 5. Negativity is recognized as a favourable factor for outcome before ASCT. The persistence of residual positivity is a variable of incomplete significance in patients still responding or stable based on CT scan evaluation. Different metrics parameters affecting outcome have been described before salvage, including high TMTV and SUV$_{\text{max}}$.

In this report concerning parameters after salvage chemotherapy, the quantitative metric of TMTV was not as prognostic as SUV$_{\text{max}}$. This finding could be explained by bias inherent in patient selection; only patients with low-volume residual disease would be considered for ASCT. Without sufficient variation in the volume of disease between patients, TMTV may be less useful for risk stratification. SUV$_{\text{max}}$ values were more evenly distributed. Thus, in most patients harbouring low-volume disease, metabolic activity on PET may be a better discriminatory parameter compared to tumour measurements.

Evolution of tumour mass and PET parameters reflect chemosensitivity. Despite robust criteria of response, grey zones still exist, and the quality of the response can affect treatment decisions. Until recently, no alternative to ASCT was available. The benefits obtained with CAR-T in rr DLBCL patients failing first- and second-line therapies included modifying the strategy. If the judgement for the population under study fails, it seems acceptable to propose direct salvage with CAR-T. However, in this report, a less pessimistic approach can be proposed in patients with PR and SD with a low SUV$_{\text{max}}$ (<11) and a DS of 4 (Figure 4). Even if a residual mass TMTV of less than 30 ml is noted, consolidation with ASCT can yield sustained five-year PFS in 40% of patients, with 54% OS. The median OS for patients with a high SUV$_{\text{max}}$ was 0.9 years (95% confidence interval 0.5–not available), and that for patients with a low SUV$_{\text{max}}$ was 11.3 years. These data are consistent with the data obtained from patients included in the CORAL study with SD and PR who underwent transplantation. A recent registry-based analysis reported on 266 PR patients before transplant with a two-year PFS of 52% and an OS of 69%. The relapse rate is still high and warrants alternative approaches. Defining this subgroup will help to recognize patients still eligible for ASCT or those who should be challenged by new approaches in prospective studies. These data suggest the need for a randomized study on relapsed patients still in PR after chemoimmunotherapy before ASCT.

Registry data now include long-term follow-up data. The percentage of cured patients after ASCT is evaluable at 10 years, whereas data for CAR-Ts remain immature. The evaluation of new approaches with bispecific monoclonal antibodies or new CAR-Ts is promising, but randomized studies with long follow-ups are necessary. In summary, a significant proportion of patients with rr DLBCL with residual disease PET and after salvage chemotherapy can still experience durable remission after ASCT consolidation.

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