Editorial Commentary | Palliative Medicine and Palliative Care for Incurable Cancer

Axi-cel as a safe and effective treatment in older patients with large B-cell lymphoma

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In April 2022, the CD19-directed chimeric antigen receptor T-cell (CAR-T) product axicabtagene ciloleucel (axi-cel) was Food and Drug Administration (FDA) approved in 2nd line for relapsed/refractory (r/r) large B-cell lymphoma (LBCL). This was based on results from the global Phase III ZUMA-7 study which demonstrated improved event-free survival (EFS) (1) and more recently improved overall survival (OS) (2) compared with standard of care (SOC) intensive chemo-immunotherapy and autologous stem cell transplantation (ASCT) in patients with r/r LBCL within 12 months of 1st line chemo-immunotherapy.

The role of ASCT consolidation as SOC in chemo-sensitive r/r LBCL at 2nd line has been established for several decades. This was initially supported by the findings of the PARMA (3) trial, conducted in the pre-rituximab era, which demonstrated a 34% improvement in 5-year EFS with ASCT consolidation relative to further cycles of salvage chemo-immunotherapy. More recently, the CORAL (4) and LY.12 (5) trials substantiated this approach. However, there are many limitations with this strategy. Only 50% of r/r LBCL patients are considered eligible for ASCT, many limited by older age (6), impaired physical fitness and organ dysfunction. Of those deemed eligible, ASCT is often precluded by a poor response to salvage chemotherapy. Of note, the CORAL and LY.12 trials highlighted poorer outcomes with SOC in the subgroup of patients with primary refractory disease and/or relapse within 12 months of diagnosis, with only 25% of such patients in the LY.12 trial responding to salvage therapy and proceeding to ASCT (7).

In light of the dramatic increase in life expectancy over the past 50 years, the fact that half of newly diagnosed lymphoma cases are over the age of 65 and that ASCT outcomes have been shown to be inferior in older cohorts (8,9) [especially in the early post-transplant period (10)], access to potentially curative therapies for older patients with r/r LBCL has been long awaited.

Older age alone does not preclude patients from CAR-T therapy. Pivotal trials leading to FDA approval of the most widely used CAR-T commercial products in 3rd line did not mandate an upper age limit, e.g., in the ZUMA-1 (11) and JULIET (12) studies the median patient age was 58 and 56 years, with 24% and 23% of patients respectively over the age of 65 years. Further, ZUMA-1 subgroup analysis at 2 years of follow-up showed that older patients were just as likely as younger patients to achieve durable responses, with a manageable safety profile (13). Real-world evidence (RWE) confirms this finding in older patients (14-17), albeit

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with the suggestion of more frequent high-grade toxicity, especially neurotoxicity (15,17,18).

Indeed, certain real-world analyses have even reported favourable overall response rate (ORR) among the older cohorts compared to their younger counterparts, although it is important to acknowledge that stringent patient selection criteria in this group may have influenced these results (17). However, despite the overall improved outcomes, the real-world experience reported by the German GLA/GRST group, indicated a higher 12-month non-relapse mortality (NRM) in the older cohort (9% in patients aged ≥65 *vs.* 3% in <65) (17). In those ≥65 years, Jacobson *et al.* reported a higher grade of cytokine release syndrome (CRS) [odds ratio (OR) 1.41; 95% confidence interval (CI): 1.02 to 1.94] and immune effector cell-associated neurotoxicity syndrome (ICANS) (OR, 1.77; 95% CI: 1.39 to 2.26) in a large real-world study involving over 1,000 patients from 78 centres (15). Additionally, other large registry analyses focused on the commercial use of CAR-T therapies, including axi-cel or tisagenlecleucel (tisa-cel) corroborated this finding (16,17). Furthermore, some authors identified a linear association between age and any grade ICANS, particularly affecting patients over the age of 65 (16), noting that this cohort included patients infused with either commercially available product.

Until recently, there has been limited data on outcomes in older patients receiving axi-cel in the 2nd line setting, but Westin *et al.* have now reported efficacy and toxicity outcomes in older (≥65 years) patients on the ZUMA-7 study as part of a pre-planned subgroup analysis (19). One-hundred and nine patients met the age cut-off for this sub-group analysis (median 69 years, range, 65–81 years) and almost half of the patients were over the age of 70 years. Patient baseline characteristics in the axi-cel and SOC arms were well-balanced for age and response to 1st line treatment, although the axi-cel group was enriched for known high-risk characteristics such as higher score for second line age-adjusted International Prognostic Index (sAAIPI) (53% *vs.* 31%), elevated lactate dehydrogenase (LDH) (61% *vs.* 41%) and high-risk molecular "hits" including MYC with BCL2 or BCL6 rearrangement (24% *vs.* 12%).

Treatment feasibility was also reported. Despite older age, there were no axi-cel manufacturing failures. Axi-cel was successfully infused in 96% and 92% of all patients and patients >70 years respectively. In contrast, only 33% of all patients and 22% of patients >70 years randomized to the SOC arm reached ASCT due mainly to lack of response to intensive salvage chemo-immunotherapy.

Toxicity tolerance is also an important factor in determining the relative merits of CAR-T *vs.* ASCT. Westin *et al.* show that the incidence of severe (≥ grade 3) CRS and ICANS was 8% and 27% respectively in the older cohort, which is higher than in the overall ZUMA-7 patient population (6% and 21%) (1), but similar to that reported in all patients treated at 3rd line or beyond in the pivotal ZUMA-1 (11) trial and in real-world analyses (15).

The authors have also reported CAR-T cell expansion kinetics as well as inflammatory cytokine repertoire. CAR-T expansion on ZUMA-7 was similar in the older subgroup compared with their younger counterparts and most baseline markers of inflammation did not significantly differ between the groups. In contrast, peak inflammatory serum and cytokine markers were significantly higher in the older patient subgroup, which may explain the slightly higher incidence of immunotoxicity.

With respect to cytopenias, the incidence of severe neutropenia was higher in the patients who received axi-cel *vs.* SOC (80% *vs.* 44%), as was prolonged neutropenia beyond 90 days post infusion (10% *vs.* 5%).

Nevertheless, the incidence of severe sepsis (≥ grade 3) was more than double in the SOC group (2% *vs.* 5%). The utilization of tools recently added in the CAR-T physicians' armamentarium such as the CAR-HAEMATOTOX score (20) may prove useful in the risk-stratification, prevention and management of this important toxicity in this vulnerable group.

The number of deaths was similar between cohorts (43% patients in axi-cel arm *vs.* 47% patients in SOC arm) mainly due to progressive disease (PD) (axi-cel arm: 19/21 PD, SOC arm: 20/25 PD). No treatment-related fatal adverse events (AEs) were reported in axi-cel patients and there was one fatal event in the ASCT cohort. Broadly, the toxicity profile of axi-cel was similar to that observed in previous studies with no new serious/fatal AEs observed.

ORRs in this ZUMA-7 sub-analysis were significantly higher in the axi-cel versus SOC arms (88% *vs.* 52%), with axi-cel patients twice as likely to achieve complete response (CR) than SOC patients. Median EFS and progression-free survival (PFS) were 8- and 4-fold longer in the axi-cel arm (21.5 months EFS and PFS) *vs.* the SOC arm (2.5 and 5.0 months) respectively. Importantly, both EFS and PFS advantage maintained significance on multivariate analysis after adjusting for differences in cohort baseline characteristics. Similar response rates were observed and similar EFS and PFS estimations were made in the >70 sub-

cohort analysis. Axi-cel-infused patients on this ZUMA-7 subgroup analysis had prolonged OS compared to SOC patients [hazard ratio (HR) 0.517; 95% CI: 0.277–0.964], even when SOC patients crossed over to subsequent off-protocol CAR-T cell therapy (57% of ZUMA-7 SOC arm patients crossed over). Although these latter results did not reach statistical significance, it is quite likely that the data are not mature enough by this current data cut-off, and future evaluations may be helpful to further elucidate this. Reports on extended follow-up of the ≥65 years cohort are keenly awaited to confirm whether a survival benefit with axi-cel *vs.* SOC emerges, similar to that observed by Westin *et al.* in all patients on ZUMA-7 (2).

Quality of life (QoL) and patient reported outcome (PRO) measures were of key importance in this study. Although there was an initial parallel drop in patient-reported outcomes for QoL, physical functioning and global health status during the early post-treatment period for both axi-cel and SOC, this recovered quickly and steadily after day 100 (D100) in the axi-cel group and exceeded the corresponding baseline scores. On the other hand, these scores did not recover as quickly in the SOC arm, and were never superior to baseline.

Overall, this study shows that in older patients, axi-cel in 2nd line, when compared with SOC, is feasible and confers improved efficacy and meaningful improvements in QoL, alongside a manageable toxicity profile, rendering it a promising, potentially curative option for patients who have previously faced therapeutic limitations. Although at this point a statistically significant OS benefit in those ≥65 years has not been demonstrated, up-to date analyses are underway. With more CAR-T approvals in 2nd line (21), alongside recently reported and ongoing studies focusing on 2nd line treatment of LBCL in older and/or transplant ineligible patients by non-age criteria, such as ALYCANTE (NCT04531046) (22) and PILOT (NCT03483103), the future therapeutic landscape may be one where age is no longer a barrier and CAR-T is the key player in the management of relapsed LBCL among the geriatric cohort. Nevertheless, the success of such a paradigm shift in the therapeutic landscape of older patients is likely to rely on judicious patient selection, comprehensive assessment of existing comorbidities, pre-treatment fitness optimization ("pre-habilitation"), early and robust toxicity management and optimal supportive care (23). With appropriate multidisciplinary input, older age may no longer be an impedance to curative outcomes in patients with relapsed LBCL.

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