Editorial Commentary | Palliative Medicine and Palliative Care for Incurable Cancer

Comparing axi-cel and standard of care in relapsed/refractory large B-cell lymphoma: a review of recent data on Q-TWiST, survival insights, and chimeric antigen receptor T-cell therapy considerations

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CD19 chimeric antigen receptor T-cell (CAR-T) therapeutics are widely used for relapsed/refractory (R/R) B-cell malignancies, including acute lymphoblastic leukemia (ALL), large B-cell lymphoma (LBCL), mantle cell lymphoma (MCL), and follicular lymphoma (1). In Europe, tisagenlecleucel (commercially known as Kymriah and developed by Novartis) and axicabtagene ciloleucel (marketed under the name Yescarta and produced by Kite) represent distinct CAR-T therapies, each possessing a unique set of approved therapeutic indications. Specifically, tisagenlecleucel is authorized for employment in cases of R/R ALL in pediatric and young adult patient populations, as well as for the treatment of R/R diffuse LBCL (DLBCL). Conversely, axicabtagene ciloleucel (axi-cel) has received regulatory approval for its use in managing R/R high-grade B-cell lymphoma and primary mediastinal B-cell lymphoma (2).

DLBCL is the most common lymphoma histological subtype with about one-third (32.5%) of lymphoma patients. It consists generally of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) chemo-immunotherapy, and Pola-R-CHP (polatuzumab vedotin, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) (3). First-line treatment may produce 3-year overall survival (OS) and progression-free survival (PFS) of 80% and 75%, respectively (4). The standard of care (SOC) for relapsed DLBCL patients had previously been platinum-based salvage chemo-immunotherapy, such as R-CARBO-DHAP (rituximab plus carboplatin and dexamethasone, high-dose cytarabine, cisplatin), R-ICE (rituximab plus ifosfamide, carboplatin, and etoposide) or similar regimens, followed by autologous stem cell transplantation where appropriate. Recently, CAR-T cell therapies have demonstrated improved response rates and improved survival in patients with R/R DLBCL. The ZUMA-7 trial (NCT03391466) and the TRANSFORM trial (NCT03575351), are two multinational phase 3 randomized trials, that demonstrated superiority of axi-cel and lisocabtagene maraleucel (liso-cel), over salvage chemotherapy followed by autologous stem cell transplantation in terms of event-free survival (EFS) time and response rates among patients with R/R LBCL (5,6). These landmark trials have contributed to reshaping

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the treatment landscape for R/R LBCL by showcasing the efficacy of CAR-T therapy as a viable and beneficial alternative.

The Q-TWiST (quality-adjusted time without symptoms or toxicity) methodology offers a comprehensive framework for the comparative evaluation of treatments. It delineates the OS time into separate health states, effectively accounting for both the impact of treatment-related toxicity and the progression of the disease itself. The adapted Q-TWiST analysis presented in Kersten *et al.* [2023] study entitled "Quality-Adjusted Time without Symptoms or Toxicity: Analysis of Axicabtagene Ciloleucel versus Standard of Care in Patients with Relapsed/Refractory Large B Cell Lymphoma" provides insights into the quality-adjusted survival duration of individuals with R/R LBCL who have undergone treatment with axi-cel, in contrast to the SOC (7). Most of methods presented in this article were original and/or well adapted for CAR-T cell treatment in settings of LBCL. Results seem also to be in line with historical data in similar scenarios. The preplanned analysis of OS was partitioned into three mutually exclusive health states: time with grade ≥3 adverse events before the event as defined in the EFS analysis (TOX), time without severe toxicity before the event (TWiST), and time after the event (REL). It is worth mentioning that the weighing method, state specific quality of life (QoL) utility value (U, ranging from 0 to 1), assuming a base case U(TOX) =0.5, U(REL) =0.5, appears adequate considering the specificity of treatment in this group of patients with R/R LBCL (7). Axi-cel demonstrated its strength as a therapy through a marked increase in quality-adjusted survival. The relative Q-TWiST gain of 21.9%, recognized as "clearly clinically important", underscores the practical significance of axi-cel. This finding places axi-cel among the top-performing therapies, as indicated by its substantial Q-TWiST gain. Particularly worthy, is its increased efficacy in patients aged 65 years and older, which often face limited choices. The paper's recognition of treatment-related adverse events and risk-benefit trade-off are essential for understanding the complex interplay between efficacy and toxicity endpoints. As a result, this paper presents as a valuable resource for clinicians and researchers aiming to optimize treatment strategies for patients with R/R LBCL.

However, it is crucial to recognize certain considerations and limitations that warrant attention.

Firstly, the study assumes conventional utility values for different health states, which may not accurately reflect individual patient preferences. Patient preferences for avoiding toxicity or disease progression can vary widely, and employing fixed utility values might oversimplify the complex decision-making process in real-world clinical practice. The Q-TWiST methodology utilized in the analysis provides a comprehensive framework for comparing treatment outcomes in terms of quality-adjusted survival time, considering both the duration and quality of time spent in different health states. It is important to explore additional factors that can influence patient preferences and decision-making. Factors such as treatment cost, accessibility, and long-term follow-up care can significantly impact the perceived benefits and risks associated with axi-cel and SOC. Integrating these aspects into the analysis would provide a more holistic perspective on the overall value of each treatment option.

It is imperative to recognize that, despite demonstrating enhanced EFS with axi-cel, the availability of data pertaining to long-term survival outcomes is still unfolding. Importantly, in the context of axi-cel, substantial long-term OS data were already accessible as early as 2017, originating from the pivotal ZUMA-1 trial (NCT02348216). This trial investigated axi-cel in patients with R/R LBCL and reported notable findings, including a median OS of 25.8 months, an estimated 5-year OS rate of 42.6%, and a disease-specific survival estimated at 5 years of 51.0%. These figures constitute a critical element for consideration. The evaluation of response durability and OS achieved with axi-cel in comparison to platinum-based salvage chemotherapy followed by autologous stem cell transplantation over extended follow-up periods assumes a pivotal role in the comprehensive assessment of the treatment's long-term advantages and potential risks. In this context, it is important to emphasize the principles, of person-centered care which prioritizes the consideration of individual patient values, preferences, and goals when making treatment decisions. By incorporating this perspective, the analysis evaluates how well axi-cel and SOC align with the principles of person-centered care. Assessing the extent to which these treatments allow patients to maintain autonomy, engage in shared decision-making, and achieve their personal health-related goals would provide valuable insights into the patient-centeredness of these interventions.

It is important to acknowledge that the sole reliance on Q-TWiST analysis may offer an incomplete portrayal of the patient experience to LBCL treatment, particularly in terms of health and well-being. While the analysis provides a quantitative assessment of quality-adjusted

survival time, it does not encompass the qualitative aspects of patient well-being and the impact of treatment on daily life. To obtain a more comprehensive understanding of the benefits and drawbacks of axi-cel and SOC, it is crucial to consider patient-reported outcomes, such as symptom burden, functional status, and emotional well-being. For instance, the study conducted by Johnson *et al.* [2023] demonstrated that health-related quality of life (HRQoL) in patients undergoing CAR-T therapy for R/R LBCL initially experienced a decline within the first 30 days, but there were indications of potential improvement after 6 to 12 months (8). Moreover, the study by Sidana *et al.* [2022] revealed that while all groups, including those undergoing CAR-T therapy, initially encountered a short-term decline in QoL, physical and functional well-being were notably less in the CAR-T therapy group when compared to the stem cell transplant groups (9). Additionally, incorporating patient narratives and qualitative data would provide valuable insights into the lived experiences of individuals undergoing these treatments, enriching the analysis, and informing clinical decision-making.

Finally, CAR T-cell therapies like axi-cel can be expensive and may have logistical challenges associated with manufacturing and administration, specifically in low-income countries. These factors can influence the accessibility and widespread adoption of such treatments, potentially limiting their use in certain healthcare settings or regions. This assertion is corroborated by the findings of Lin *et al.* [2019], which demonstrated a lack of cost-effectiveness, primarily due to the significantly elevated incremental cost-effectiveness ratio (ICER) surpassing the established willingness-to-pay (WTP) threshold (10). Furthermore, it is significant to note that while toxicities, adverse events, and efficacy may appear similar on a broad level, there exists intrinsic qualitative variability within the same CAR-T therapies and variation exists between different CAR-T therapies. This observation underscores the need for a more nuanced and comprehensive evaluation of the Q-TWiST analysis methodology, thereby encouraging researchers to conduct similar investigations across different CAR-T therapies. This approach allows for a more accurate assessment of the full spectrum of outcomes and considerations in the field of cellular immunotherapy.

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