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Management Considerations for Primary Refractory Large B-cell Lymphoma

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Description

Different definitions of "primary refractory" have been used in clinical practice and in clinical trials for diffuse Large B-cell Lymphoma (LBCL). Recently, survival outcomes in two United States of America prospective groups were reported, representing the largest analysis of patients with primary refractory LBCL to date [1]. This study showed inferior outcomes for patients with no response, Stable Disease (SD) or Progressive Disease (PD) during or by the end of frontline therapy, compared to patients with a Partial Response (PR) at the end of treatment or those with an early relapse after initial Complete Response (CR). We propose this as the best definition of primary refractory LBCL to highlight patients in need of distinct management [1]. In 2021, two anti-CD19 Chimeric Antigen Receptor T-cell Therapies (CAR-T) Axicabtagene ciloleucel (axi-cel) and Lisocabtagene maraleucel (liso-cel) demonstrated an Event Free Survival (EFS) benefit compared to the historical standard of Autologous Stem Cell Transplant (ASCT) for patients with primary refractory or early relapsing disease, defined as relapse less than 12 months from frontline chemoimmunotherapy [2,3]. While CAR-T will undoubtedly have a positive impact on long term survival outcomes for these patients, achieving disease control prior to this therapy and efficiently navigating logistics of CAR-T still remains a challenge and an unmet need for those with primary refractory disease.

At the time refractory disease is suspected, the treating clinician should obtain a biopsy to confirm refractory disease and concurrently refer to a clinician with expertise in cellular therapy for patients with lymphoma. CAR-T represents the only curative treatment option for these patients and is the clear standard of care for eligible patients. Even for patients initially treated at academic centers, time spent confirming CAR-T eligibility, obtaining insurance approval, undergoing leukapheresis and waiting for CAR-T manufacturing can take 1-2 months. This time frame may be significantly lengthened for patients needing a referral to an academic center. Primary refractory patients by this new definition have either residual or progressive disease, which means patients are likely symptomatic and may have high tumor burden from not having achieved good disease control from frontline immunochemotherapy. Expediting referral and CAR-T process for these patients is critical.

The majority of primary refractory patients will need bridging therapy prior to CAR-T. A lower tumor burden has been associated with improved outcomes to CAR-T and less rates of Cytokine Release Syndrome (CRS) but unlike patients undergoing ASCT, a CR is not necessary [4]. If possible, we recommend leukapheresis prior to bridging therapy. For all patients, we recommend close monitoring of disease status pre-CAR-T with frequent imaging/laboratory assessment to ensure response to bridging therapy. There is currently no preferred approach to bridging therapy. For patients with progression through frontline immunochemotherapy, we recommend consideration of clinical trials with allogeneic CAR constructs or novel targeted therapy combinations (Figure 1). Therapy with common salvage chemotherapy regimens such as R-ICE, R-DHAP, R-GemOx have low Overall Response Rates (ORR)[1] and we recommend the use of targeted therapies such as tafasitamab/lenalidomide or loncastuximab-tesirine, though notably even these regimens have ORRs less than 50% and there remains an unmet need for effective second line (2L) therapies for primary refractory patients [5]. For patients who have had some disease response but ultimately residual or progressive disease at the end of treatment, salvage regimens may be used but we do not recommend giving for more than 1-2 cycles with short interval disease re-assessment. Polatuzumab-vedotin (Pola)-Bendamustine, Rituximab (BR) has demonstrated promising data as a bridging therapy [6] and would be recommended for patients who received R-CHOP as frontline therapy, but is anticipated to be less effective for patients who have been treated with Pola, rituximab, cyclophosphamide, doxorubicin and prednisone (Pola-R-CHP) as their frontline regimen and bendamustine is typically avoided pre-apheresis given significant lymphodepletion that can occur with this agent. For patients with bulky disease or disease located in one region, we recommend the use of Radiation Therapy (RT) [7]. While CD20 × CD3 Bispecific antibodies (BsAb, glofitamab or epcoritamab) are emerging as a promising treatment for Relapsed/Refractory (R/R) LBCL [8,9] and there is increasing use as a bridging therapy, there are concerns that initiating prior to apheresis could result in decreased T-cell fitness in the apheresed CAR-T product, though data remain limited. For patients who are ineligible for CAR-T, clinical trials remain a preferred option but single agent BsAbs or BsAb combinations will likely emerge as a key therapy for this population (Figure 1).

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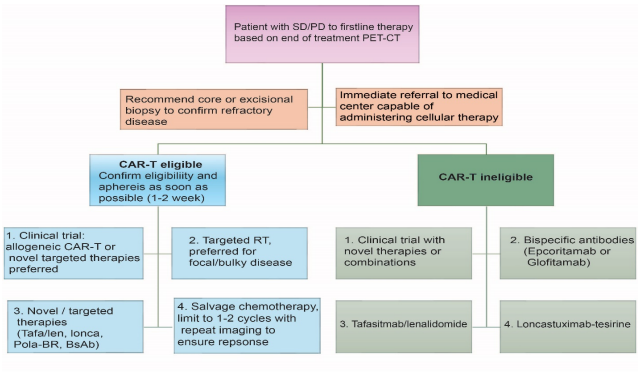

Figure 1: Management considerations for primary refractory large B-cell lymphoma.

Conclusion

Primary refractory patients are a challenging group of patients with R/R LBCL to manage and have historically had poor outcomes with an OS of less than 6 months after relapse. The approval of CD19 CAR-T therapies in the 2L gives these patients hope of a long-term cure, but significant challenges remain in both universal access to this therapy and selection of treatment regimens to achieve disease control in a population of patients who usually have highly symptomatic and rapidly progressive disease. Distinguishing patients with primary refractory disease, as defined by Bock and co-authors to be patients with SD/PD by the end of treatment will identify patients for expedited referral to medical centers capable of delivering CAR-T and those who would most benefit from clinical trials investigating allogeneic CAR constructs or targeted 2L therapies.

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