Practical Hematologist

Treating Relapsed/Refractory DLBCL: Practice Implications

Matthew Lunning, DO, FACP
Associate Professor, Division of Oncology & Hematology
Assistant Vice Chancellor of Clinical Research
Associate Vice Chair of Research
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

TAKE-HOME MESSAGES

- CAR T-cell therapy is now an option in primary refractory and early first relapse DLBCL.
- Autologous transplant remains an option for late relapse (>1 year after completion of induction therapy)
- Multiple agents are now available, but there are only limited data on sequencing before or after

The treatment of diffuse large B-cell lymphoma (DLBCL) is a success story of modern oncology, and most people can be cured. Dr. Lunning discusses key data from recent publications and conferences on current and emerging approaches for the treatment of patients whose DLBCL failed to respond to standard therapy.

Why cellular therapies?

Several cellular therapies are now on the market and many more are in phase 1 and 2 trials. Chimeric antigen receptor (CAR) T-cell therapy or cellular therapy is an important part of the management of relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). Although approximately 60% to 70% of patients with DLBCL are cured with the first-line chemoimmunotherapy rituximab-CHOP, the prognosis is quite poor for patients who have primary refractory disease or have refractory disease after two lines or more of therapy, or for patients who have relapsed within 12 months of an autologous stem cell transplant. As seen in the SCHOLAR-1 data, the median survival of these patients is only about 6 months.[1]

CAR T-cell treatment is now well enough established to consider it in the second-line setting. Dr. Lunning commented that when I think about a patient with relapsed/refractory disease, I used to ask myself, are these patients eligible for an auto-transplant? Now I'm asking myself, are these patients eligible for CAR T-cell therapy or another therapy?

CAR T-cell therapy for R/R DLBCL

ZUMA-7: Axi-cel vs. standard-of-care

The ZUMA-7 trial, compared axicabtagene-ciloleucel (axi-cel), a CD19 CAR-modified T-cell product, to standard of care (SoC) as second-line therapy in primary refractory or early relapsed DLBCL.[2] Patients randomized to axi-cel did not receive bridging therapy, whereas the patients in the SoC arm were treated with second-line chemotherapy and, if they had a response and were candidates for transplant, proceeded to receive an autologous stem cell transplant.

The primary endpoint of event-free survival (EFS) favored axi-cel with a hazard ratio of 0.39, and the two-year EFS was 40.5% compared to 16.3% in the SoC arm. The estimated overall survival at 2 years was slightly higher in the axi-cel group than in the SoC group but longer follow-up will be needed to determine whether this trend continues.[2]

TRANSFORM: Liso-cel vs. standard-of-care

The TRANSFORM trial was similar and compared lisocabtagene maraleucel (liso-cel) to SoC. In this trial, patients could receive bridging chemotherapy in the experimental arm and then go on to receive the liso-cel CD19 CAR-modified T-cells. The CAR T-cells were manufactured for all patients and if progression occurred in the SoC arm, they could cross over to receive liso-cel therapy as well. The median follow-up was 6.2 months, shorter than in the ZUMA trial, but EFS in the liso-cel arm showed a clear benefit of 10.1 months compared to 2.3 months on SoC, as well as a trend towards a difference in survival rates.[3]

PILOT: Liso-cel for patients who were ineligible for stem cell transplant

Ineligibility for transplant was defined by many different criteria but at least one of the following had to be present: age >70 years, ECOG performance status of 2, DLCO of <60%, LVEF between 40 and 50%, or a creatinine clearance between 30 to 60 ml/min.[4] The overall response rates (ORR) were in the 70-80% range and complete remission (CR) rates between 50 to 60%.

> "Some individuals think that, if you're not a transplant candidate, then you're no longer a CAR T-cell candidate. The PILOT trial really challenged that."

Transitioning CAR T-cell therapy to the commercial environment

According to Dr. Lunning, only one in five patients who could get CAR T-cell therapy is actually getting it. He distinguishes between two phases that impact the timeline: the "brain-to-vein time" and the "vein-to-vein" time. He says that there are certain hurdles that exist in the brain-to-vein time before apheresis is even started, including the need for prior authorization, negotiation of single case agreements, and allocation of apheresis slot time. The vein-to-vein time, or the time taken between the apheresis of the T-cells to reinfusion, is important in clinical trials and needs to be incorporated into the evaluations of outcomes metrics. Although processes exist to bridge the time between apheresis and infusion of the T cells, the brain-to-vein time needs to be shortened or bridged as well.

He also mentioned that outcomes could be better, especially in high-risk populations, possibly by finding adjunctive therapies to improve the CAR T-cell products. Other unresolved issues are how to handle early or late CAR T-cell failures and to understand the mechanisms leading to these failures.

Other treatment options for R/R DLBCL

Polatuzumab/Bendamustine/Rituximab vs. Bendamustine/Rituximab

This was a small, randomized, phase 2 trial evaluating the addition of polatuzumab, a CD79b-directed antibody-drug conjugate, to bendamustine/rituximab. The ORR and the CR rates were much higher in the polatuzumab/bendamustine/rituximab arm compared to the bendamustine/rituximab arm (45% vs. 18%, and 40% vs. 18%, respectively), and, surprisingly, the trial also showed an overall survival advantage for the triple combination (12.4 months vs. 4.7 months).[5] A larger expansion study confirmed these findings with a median PFS of 6.6 months for the triple combination and an OS of 12.5 months. Based on these results, polatuzumab, in combination with bendamustine and rituximab, was approved by the FDA for the treatment of R/R DLBCL, and the NCCN guidelines allow for polatuzumab with or without bendamustine and with or without rituximab. Dr. Lunning says that now his #1 bridging strategy in the pre-apheresis period is to give polatuzumab as a single agent or polatuzumab/rituximab if the tumor is still rituximab-sensitive.

RE-MIND studies: a model for the analysis of data

The results from the initial study (L-MIND) of tafasitamab, a CD19 antibody, paired with lenalidomide or an immunomodulatory agent in transplant-ineligible patients with R/R DLBCL, were compared to real-world data of lenalidomide monotherapy (RE-MIND study) by matching them by disease characteristics.[6] In this retrospective analysis the combination of tafasitamab/lenalidomide demonstrated a significantly better ORR of 67.1% compared to 34.2% for lenalidomide monotherapy, as well as higher CR and survival rates.[6]

In Re-MIND2 this analysis was extended to comparisons of tafasitamab/lenalidomide with several other treatments, including systemic therapy, bendamustine/rituximab (BR), and the combination of rituximab/gemcitabine/oxaliplatin (R-Gem-Ox). Significant differences were found in ORR, as well as CR and OS rates when compared to systemic, BR, or R-Gem-Ox therapy.[7] Dr. Lunning concluded tafasitamab/lenalidomide has replaced lenalidomide/rituximab in the R/R DLBCL space. Data evaluated in this retrospective fashion provide interesting support regarding the potential utilization of tafasitamab/lenalidomide over chemoimmunotherapy in patients who have previously been refractory to chemoimmunotherapy.

LOTIS-2: Loncastuximab tesirine

Loncastuximab tesirine, or Lonca-T, is an antibody-drug conjugate against CD19 B cells. It carries a novel pyrrolobenzodiazepine warhead, distinguishing it from other drugs. It is given at a higher dose for the first two cycles, and then the dose is halved, and supportive measures are used to reduce the risk of pleural effusions or edema that have been seen with different dosing schedules.

LOTIS-2, a single-arm, phase 2 trial in patients with R/R DLBCL, showed an ORR of 48.3% in all patients with a CR rate of 24.1%. For those patients whose tumor did respond, there is the potential for durability with the median not yet reached at the time of data cut-off. The main side effect was peripheral edema and pleural effusions, managed with dexamethasone. An isolated elevation of GGT without significant liver abnormalities was seen as well but its significance is unknown at this time.[8]

Discussion

Do subset classifications matter when making treatment decisions in R/R DLBCL?

Dr. Lunning responded that ZUMA-7 data showed that cellular therapy or CAR T-cell therapy directed at CD19, has been agnostic to molecular features.

What should be considered when using some of these emerging therapies?

Giving a CD19 monoclonal antibody or a CD19 antibody-drug conjugate, especially if planning to apherese a patient for CAR T-cell therapy in the next 30 to 60 days, should be done with caution, notes Dr. Lunning. In vivo data show down-regulation of the CD19 antigen on the cell surface after the use of such agents as tafasitamab, and it might be necessary to wait for about 100 days until CD19 recovery occurs.

> "I don't really know that there's a significant amount of data of one of those agents with apheresis and then reinfusion of CAR T-cells to know what to do in that situation. However, if that therapy is felt to be necessary to keep the individual alive, I might use polatuzumab either for pre-apheresis or post-apheresis bridging."

Are there patients that should not be considered for CAR T-cell therapy?

As per Dr. Lunning, there is no clear-cut answer to this question, except not to offer CAR T-cell treatment to a person whose tumor is refractory to another CD19 CAR T-cell product. However, there is a need for clinical trials to explore different cellular therapies, potentially with a distinct mechanism, either another construct or a second antigen that then could target CD19 and CD20, or CD19 and CD22.

Performance status may be a situation where a patient should be excluded from consideration for CAR T-cell therapy. However, performance status is often very subjective. If the performance status is poor due to disease characteristics, it might be worthwhile having a risk-benefit discussion with the patient about proceeding or not. On the other hand, if the performance status is due to comorbidities not related to the lymphoma and there is concern that even a low-grade CRS (cytokine release syndrome), or ICANS (immune effector cell-associated neurotoxicity syndrome) would be significantly detrimental to the quality of life or potentially even be lethal, the patient should be advised against CAR T-cell therapy.

Does radiotherapy still play a role in these situations?

According to Dr. Lunning there is a dearth of data in this area. However, there might be an indication in patients with bulky disease, where CAR T-cells might not work well.

> "I use the analogy of peeling an onion. You've got to get all the way to the core of the onion in order to eradicate the disease. If an initially bulky lesion becomes PET negative and was reduced by 50% or more, I may have the discussion about post-CAR T-cell radiation with the patient because I am concerned that that's the area where the CAR T-cells are struggling to get to the core."

Will the bispecific antibodies replace CAR T-cell therapy in the future?

Dr. Lunning says that he is not sure that they will replace CAR T-cell therapy since they inhibit different targets. However, what is not known is the fitness or the fidelity of the T-cells in a patient who progresses through bispecific antibody therapy, possibly complicating the manufacturing of CAR T-cells. There is emerging data with bispecifics after CAR T-cell therapy but the use before CAR T-cell therapy should best be done in clinical trials.

Should CAR T-cell therapy be used instead of palliative care?

It depends on what the reason to consider palliative care is, says Dr. Lunning. If it is the disease itself, and not some serious comorbidity, it is probably worth having that discussion with the patient.

> "Is it worth that to them? Is the commitment worth it to the family? CAR T-cell therapy is a logistical process. It means being away from your home, your farm, your community for a period of time."

Summary

CAR T-cell therapy is now an option for patients with large B cell lymphoma that is primary refractory or in early first relapse, while autologous transplant remains an option for late-relapse DLBCL. Multiple agents for relapsed/refractory DLBCL are available, however, there are currently only minimal data on sequencing, including their use before or after CAR T-cell therapy.

To view the associated accredited activity please **click here**.

References

1. Crump M, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. Oct 19 2017;130:1800-1808. doi:10.1182/blood-2017-03-769620

2. Locke FL, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med*. Feb 17 2022;386:640-654. doi:10.1056/NEJMoa2116133

3. Kamdar M, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet*. Jun 18 2022;399:2294-2308. doi:10.1016/s0140-6736(22)00662-6

4. Sehgal A, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. *Lancet Oncol*. Aug 2022;23:1066-1077. doi:10.1016/s1470-2045(22)00339-4

5. Sehn LH, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. *Blood Adv*. Jan 25 2022;6:533-543. doi:10.1182/bloodadvances.2021005794

6. Zinzani PL, et al. RE-MIND: Comparing Tafasitamab + Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma. *Clin Cancer Res*. Nov 15 2021;27:6124-6134. doi:10.1158/1078-0432.Ccr-21-1471

7. Nowakowski GS, et al. Improved Efficacy of Tafasitamab plus Lenalidomide versus Systemic Therapies for Relapsed/Refractory DLBCL: RE-MIND2, an Observational Retrospective Matched Cohort Study. *Clin Cancer Res*. Sep 15 2022;28:4003-4017. doi:10.1158/1078-0432.Ccr-21-3648

8. Caimi PF, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. Jun 2021;22:790-800. doi:10.1016/s1470-2045(21)00139-x

Provided by MediCom Worldwide, Inc.

This activity is supported by educational grants from Bristol Myers Squibb and Genentech, a member of the Roche Group.

