Relapsed/Refractory Diffuse Large B-Cell Lymphoma and Mantle Cell Lymphoma: Is It Time to Consider CAR-T for All?

Presented by Andrew D. Zelenetz, MD, PhD

ABSTRACT

CAR T cells have demonstrated activity in relapsed/refractory non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL), indolent non-Hodgkin lymphoma, and mantle cell lymphoma. For patients with chemorefractory disease, CAR T cells can provide a durable complete response in a portion of patients, which represents a major advance in the field. For patients with chemosensitive disease, however, additional data are needed to determine whether CAR T cells are preferable to conventional approaches. Studies in DLBCL have shown that patients experiencing a PET-positive partial response after second-line chemotherapy have long-term outcomes after high-dose therapy and autologous stem cell rescue that are similar to CAR T-cell therapy, with decreased toxicity and cost. Alternative third-line options such as tafasitamab/lenalidomide and bispecific antibodies may also have a role for patients with chemorefractory disease.

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CAR T cells continue to show impressive activity in relapsed/refractory non-Hodgkin lymphoma, with durable complete responses in a significant percentage of patients with chemorefractory disease. According to Andrew D. Zelenetz, MD, PhD, Medical Director of Quality Informatics, Memorial Sloan Kettering Cancer Center, and Chair of the NCCN Non-Hodgkin Lymphoma Panel, however, for patients with chemosensitive, there is still debate about whether CAR T cells are superior to conventional approaches. At the NCCN 2020 Virtual Congress: Hematologic Malignancies, Dr. Zelenetz discussed the role of CAR T cells in diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma.

Diffuse Large B-Cell Lymphoma

Axicabtagene Ciloleucel

Axicabtagene ciloleucel was approved by the FDA for the treatment of DLBCL in 2018 based on results of the phase II ZUMA-1 trial, which included 77 patients with refractory DLBCL and 24 patients with either transformed lymphoma or refractory primary mediastinal B-cell lymphoma.¹ As Dr. Zelenetz reported, this was a population with heavily refractory disease. Nearly 70% of patients had received ≥ 2 prior treatments, 26% had primary refractory disease, and half of patients had disease resistant to 2 consecutive lines of treatment.

Every patient on trial experienced some form of adverse event, said Dr. Zelenetz. He noted that 8% of

patients died due to toxicity, and almost 90% experienced grade 3 or 4 treatment-related adverse events.

Despite the toxicity, however, this has been a highly effective treatment, he said. The objective response rate by the independent review committee was 74%, with a complete response rate of 54%. The most recent follow-up showed an ongoing response of 36%, and the median response duration has still not been reached in the independent review committee assessment.

“One of the most striking features is that after the rapid drop-off in the first 3 months, the curves for both progression-free survival (PFS) and response duration are quite stable,” said Dr. Zelenetz, who noted that expected overall survival (OS) for this group of patients would be between 10% and 15%. “Median [OS] in this study was not reached.”

According to Dr. Zelenetz, patients who experience a complete or partial response have excellent PFS, whereas those with stable disease tend to have recurrence after treatment with these agents. Patients with an ongoing response on axicabtagene ciloleucel also had a significantly greater peak T-cell expansion in peripheral blood compared with those who experienced progression or had no response to CAR T cells.

Tisagenlecleucel

Tisagenlecleucel, a 4-1BB construct targeting CD19, was approved based on data from the JULIET trial (n=111).² This study cohort consisted of a relatively young population of patients, said Dr. Zelenetz, but again represented

poor-risk patients, with >50% of patients having ≥ 3 lines of treatment and/or a history of refractory DLBCL. Although safety data showed that 100% of patients experienced some adverse event, rates of grade 3 and 4 cytokine-release syndrome were relatively low, Dr. Zelenetz reported. The risk of neurologic events was also somewhat lower than that observed with axicabtagene ciloleucel.

“The best overall response of 52%, with a complete response rate of 40%, was a little bit lower than axicabtagene,” said Dr. Zelenetz, who acknowledged that cross-trial comparisons are hazardous.

According to Dr. Zelenetz, although excellent response was seen in all groups, patients whose disease was refractory to their immediate prior line of therapy tended to have a poor response. “Not surprisingly, patients with a complete response have a better response duration and PFS compared with the entire population, but just like we saw with axicabtagene ciloleucel, those responses were durable regardless of the depth of response,” said Dr. Zelenetz. “Conversely, patients with stable disease or failure to respond on treatment did poorly.”

Lisocabtagene Maraleucel

Lisocabtagene maraleucel (liso-cel) is another CD19-directed CAR T cell that uses the 4-1BB costimulatory domain. Unlike tisagenlecleucel, however, liso-cel is a defined composition product. CD8 and CD4 T cells are independently transduced and returned to the patient in a 1-to-1 ratio.

The FDA is currently considering approval of liso-cel based on data from the TRANSCEND trial, which enrolled a heavily pretreated population of patients.³ Approximately 50% of patients had ≥ 3 prior lines of therapy, and two-thirds were refractory to chemotherapy. As Dr. Zelenetz reported, the rate of grade 3 and 4 cytokine-release syndrome was very low at only 2%. Grade 3 and 4 neurologic events were also relatively low, with only 10% of patients experiencing grade 3 and 4 toxicity.

“As this was the third anti-CD19 CAR T cell, many centers had more experience in managing cytokine-release syndrome,” said Dr. Zelenetz. He noted that 20% of patients received tocilizumab and/or corticosteroids for cytokine-release syndrome. “The first use of tocilizumab was often given when patients had only grade 1 or 2 toxicity to try to prevent the development of grade 3 and 4 toxicity.”

The objective response rate was 73%, including a complete response rate of 53% and a partial response rate of 20%, and these response were observed across different subtypes. According to Dr. Zelenetz, patients with very bulky disease were the only group that did not respond well, suggesting a role for pretreatment bridging

or cytoreductive therapy. Although patients with partial responses did not fare as well, those with complete responses have done “extremely well” with respect to duration of response, said Dr. Zelenetz.

High-Dose Therapy With Autologous Stem Cell Rescue

High-dose therapy and autologous stem cell rescue (ASCR) is the standard of care for chemosensitive relapse, Dr. Zelenetz said. However, he noted that this therapy may also have a role in treatment for patients with only a partial response after second-line chemotherapy.

A study of the CIBMTR registry evaluated chemosensitive patients who had experienced a partial response after second-line therapy. Patients were divided into 2 groups: those who experienced late chemotherapy failure (beyond 12 months) and those with early chemotherapy failure (within the first 12 months).⁴ The investigators found no difference in nonrelapse mortality. Importantly, said Dr. Zelenetz, the risk of progression plateaus at about 18 months after high-dose therapy with ASCR. This translates into a 5-year PFS of 57% and 48% for late and early chemotherapy failure, respectively.

“I believe that high-dose therapy and ASCR represents a viable alternative to CAR T cells in the setting of a partial response after second-line chemotherapy,” said Dr. Zelenetz. “Additional work needs to be done to determine whether CAR T-cell therapy in this population is superior to high-dose therapy. At this time we do not have any comparative data.”

Alternatives to CAR T Cells for Third-Line Relapsed/Refractory DLBCL

Alternatives to CAR T-cell therapy in the third-line setting exist, including the recently approved combination of lenalidomide and tafasitamab, an anti-CD19 monoclonal antibody. This combination was tested in the L-MIND study in patients who had relapsed/refractory DLBCL after 1 to 3 prior lines of treatment.⁵ Enrolled patients had to be ineligible for high-dose therapy and ASCR, and those with primary refractory disease were excluded from the study.

The overall median PFS was >12 months, said Dr. Zelenetz, but there was a “striking difference” between complete and partial responses, which resulted in an excellent OS for patients with complete response. “The durability of the complete responses is very impressive, and we hope this will hold up in future studies,” he said.

Polatuzumab Vedotin

Another option in the third line is polatuzumab vedotin, which has demonstrated an overall response rate of

approximately 50% in relapsed/refractory DLBCL. In combination with rituximab, overall response was also in the range of 50% to 60%.⁶ Importantly, however, PFS plateaus in approximately 40% of patients treated with the combination, said Dr. Zelenetz.

A randomized phase II study compared bendamustine/rituximab versus bendamustine/rituximab + polatuzumab vedotin.⁷ The overall response and complete response rates were clearly better with the addition of polatuzumab to the bendamustine/rituximab backbone, said Dr. Zelenetz, and this translated into improvements in PFS and OS. According to Dr. Zelenetz, however, questions remain regarding the necessity of bendamustine/rituximab in this regimen.

“If you’re contemplating using this as a bridge to CAR T cells, bendamustine is toxic to T cells,” said Dr. Zelenetz. “If you can avoid the use of a T-cell toxic agent, that is an important consideration.”

Mantle Cell Lymphoma

Finally, the ZUMA-2 trial explored the role of CAR T cells in mantle cell lymphoma.⁸ As Dr. Zelenetz explained, brexucabtagene autoleucel uses the same transgene as axicabtagene ciloleucel, but there is an additional T-cell enrichment step that reduces the risk of transduction of circulating CD19-expressing tumor cells.

ZUMA-2 enrolled 74 patients with relapsed/refractory mantle cell lymphoma and showed a “strikingly low” risk of grade 3 and 4 cytokine-release syndrome, said Dr. Zelenetz.

“It’s possible that we’ve gotten much better at managing this toxicity, or there could be differences in mantle cell lymphoma versus large cell lymphoma,” he suggested. “Whatever the reason, the grade 3 and 4 toxicity in the ZUMA-2 trial was clearly less than that reported in ZUMA-1.”

With robust responses observed across all subgroups, it is also a highly active agent, said Dr. Zelenetz. The overall response rate was 93%, with 67% of patients experiencing a complete response and 27% experiencing a partial response. Median response duration, median PFS, and OS have not been reached at a median follow-up of approximately 1 year. “For a group of patients with relapsed/refractory mantle cell lymphoma, this represents an exciting new treatment option,” said Dr. Zelenetz.

The NCCN B-Cell Lymphomas Panel has integrated this agent into the NCCN Guidelines for patients who have had progression or failure on Bruton’s tyrosine kinase inhibitors (see page MANT-A in the guidelines, available at NCCN.org).⁹

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Correspondence: Andrew D. Zelenetz, MD, PhD, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. Email: zeleneta@mskcc.org

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