ADVANCES IN LLM

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Recently Approved Drugs Herald a New Era in Therapy for Diffuse Large B-Cell Lymphoma

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H&O What are the standard treatments for diffuse large B-cell lymphoma (DLBCL)?

GN For nearly 20 years, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has been the standard frontline treatment for DLBCL. Some elderly patients, including those with a poor performance status or other comorbidities, may not be eligible for full-dose R-CHOP. These patients will often receive a reduced-dose version of R-CHOP (so-called mini R-CHOP) in the frontline setting. R-CHOP leads to a long-term cure in approximately 60% of patients. Patients who relapse do so relatively quickly following the initial treatment. Most patients with relapsed or refractory DLBCL will succumb to the disease. There has been much interest in the development of treatments for these patients.

The current standard of treatment is primarily based on the eligibility of patients for high-dose chemotherapy and autologous stem cell transplant. Approximately half of patients who relapse after R-CHOP are eligible for intensive salvage chemotherapy. Among these patients, approximately half will have a response that is good enough for them to proceed to high-dose chemotherapy and autologous transplant. These treatments will lead to a long-term cure in about half of patients. Ongoing clinical trials are comparing this treatment strategy with different novel treatments.

Patients who decline to undergo transplant or who are ineligible for the procedure—whether based on age, poor performance status, or comorbidities—historically have been considered largely incurable. This outcome could be changed with some of the new therapies. For these patients, the current standard is treatment with palliative chemotherapy or a recently approved agent. In contrast to frontline treatment, which has remained constant for the past 20 years, there are exciting new treatments in the relapsed/refractory setting. This field is changing quickly.

H&O What are the unmet needs in DLBCL?

GN The best chance of achieving a successful outcome in DLBCL is during first-line treatment. There is an unmet need to improve frontline treatment with R-CHOP, and there have been many attempts to do so throughout the past 20 years. No new treatments have emerged, primarily owing to issues with the design of clinical trials. Another unmet need is to develop therapies for patients who are not eligible for treatment with full-dose R-CHOP. This group includes elderly patients with organ dysfunction. There is a huge unmet need for treatments of relapsed disease, despite the recently approved therapies in this setting. Although there is a lot of excitement about chimeric antigen receptor (CAR) T-cell therapies, limited efficacy, toxicity, and access remain problems. Many patients treated in the relapsed/refractory setting will require additional therapies or will need to switch from treatment to treatment.

Another unmet need is for patients who relapse after CAR T-cell therapy. This population is particularly challenging. These patients frequently have very aggressive

disease. In addition, they often have toxicity from the CAR T-cell therapy, primarily hematologic toxicities such as cytopenias (eg, neutropenia and thrombocytopenia). These toxicities limit their ability to tolerate additional therapy or to participate in clinical trials. Several exciting novel agents are being evaluated in clinical trials, but many patients with relapsed disease after CAR T-cell therapy will not meet the standard inclusion criteria. To address this ongoing unmet need, it will be necessary to change inclusion criteria to enroll these patients into clinical trials.

H&O Are there recent insights into the pathogenesis of DLBCL that might impact treatment?

GN Traditionally, DLBCL has been divided into 2 subtypes: activated B-cell (ABC) and germinal center B-cell (GCB). The ABC subtype has been associated with a worse outcome. Many treatments for the ABC subtype act primarily via B-cell receptor signaling. We now know that the pathogenesis of DLBCL is more complex, involving the driver mutations as well as different molecular clusters. Ongoing research is evaluating whether these clusters could benefit from targeted therapies in the frontline and relapsed/refractory settings. There are 2 different broad approaches. One is trying to identify molecular drivers to develop the best targeted therapy. The other approach, which has recently gained traction, is agnostic to the molecular pathogenesis of DLBCL and targets common antigens that appear in all of the subtypes. CAR T-cell therapies, as well as other treatments that target surface markers such as CD19, are rapidly being developed. An advantage to these therapies is that they work regardless of the molecular pathogenesis of DLBCL.

H&O What are the challenges and/or opportunities in devising new treatment strategies for DLBCL?

GN The challenges and opportunities vary according to the line of therapy. In the frontline setting, the major challenge has been to select the right patients for clinical trials. In the past, hundreds of millions of dollars were spent on large trials enrolling thousands of patients in the frontline setting. Unfortunately, the results from these trials did not lead to new treatment options, and R-CHOP remains the standard of care. We now recognize some deficiencies in the original designs of those studies. There were issues regarding patient selection; the enrollment criteria frequently selected patients with a better performance status. Therefore, it was difficult to show a difference between the experimental arm and the control arm because patients in the control arm had a much better outcome than expected. These studies provided important information that was used to improve the design of new trials of frontline therapies for DLBCL. A new generation of trials incorporated design changes that will likely result in stronger data that might change the standard of care in the frontline setting.

In the relapsed/refractory setting, several drugs have been approved by the US Food and Drug Administration (FDA) in the past 3 years. These therapies can improve the response rate and durability of response, while minimizing toxicity. An interesting area of research in the relapsed/refractory space is how to sequence the available therapies. For example, CD19 is a target for several different compounds, which must be sequenced in some way. This question is a focus of ongoing research and represents an unmet need.

Relapse after CAR T-cell therapy is a challenging area of DLBCL. It is necessary to develop therapies that are less myelosuppressive. Enrollment criteria for clinical trials should encompass patients with cytopenias, which are frequently seen at the time of relapse after CAR T-cell therapy.

H&O What are some of the recently approved treatments for relapsed/refractory DLBCL?

GN The field is changing rapidly. The major breakthrough has been in cellular therapies. There are 3 different CAR T-cell products approved in this space: axicabtagene ciloleucel (Yescarta, Kite), tisagenlecleucel (Kymriah, Novartis), and lisocabtagene maraleucel (Breyanzi, Bristol Myers Squibb). These treatments have similar efficacy. At 6 months after treatment, approximately 40% of patients are in a durable remission.

There are novel antibodies and antibody-drug conjugates. In April 2021, the FDA approved loncastuximab tesirine-lpyl (Zynlonta, ADC Therapeutics), which targets CD19. Tafasitamab-cxix (Monjuvi, MorphoSys/Incyte), which also targets CD19, is approved for use in combination with lenalidomide (Revlimid, Celgene/Bristol Myers Squibb). Polatuzumab vedotin-piiq (Polivy, Genentech), which targets CD79b, is approved in combination with bendamustine and a rituximab product. Both of these drugs received accelerated approval, and they are frequently used in this setting. Another agent that received accelerated approval for relapsed/refractory DLBCL is the nuclear transport inhibitor selinexor (Xpovio, Karyopharm Therapeutics).

H&O What are some promising novel treatments?

GN There are additional antibody-drug conjugates in

clinical trials that appear promising. There are drugs that are similar to polatuzumab vedotin-piiq but that target different surface molecules. Bispecific antibodies bind the antigen on the surface of lymphoma cells on one side and the receptor on the effector T cell on the other side. These antibodies are essentially CAR T cells in a vial. The usual process of preparing the CAR T-cell product involves collection of cells from patients via apheresis. The cells are then engineered in the laboratory to express receptors that recognize targets or surface molecules on a tumor target, typically CD19. Bispecific antibodies bypass this time-consuming process. The antibody is off-the-shelf, and immediately brings the effector T cell within the proximity of the tumor cell. Several presentations at recent meetings of the American Society of Hematology showed promising activity and efficacy for bispecific antibodies in this setting. Additional studies are ongoing. It is relatively easy to combine bispecific antibodies with other therapies, which is an advantage over CAR T cells.

There are many CAR T-cell therapies in development. These new agents target multiple antigens. There is also an effort to develop off-the-shelf CAR T cells.

H&O What are some advances in the drug development process in DLBCL?

GN Tafasitamab-cxix plus lenalidomide was approved for the treatment of patients with relapsed/refractory DLBCL based on results from the L-MIND trial. An interesting aspect to this study is that it enrolled patients who developed relapsed disease after treatment with R-CHOP and who were not eligible for autologous stem cell transplant. Importantly, neither tafasitamab-cxix nor lenalidomide is approved as a single agent for the treatment of DLBCL. The accelerated approval of this doublet was also based on real-world data from a study called RE-MIND. My colleagues and I presented the RE-MIND study at the American Society of Clinical Oncology annual meeting in 2020, and results will be published shortly. Investigators in the RE-MIND study collected information from treatment centers around the world regarding the efficacy of single-agent lenalidomide in patients with relapsed/refractory DLBCL. These patients were matched for a number of covariates to patients treated in the L-MIND study. Based on this analysis, it was possible to show that the addition of tafasitamab-cxix to lenalidomide doubled the response rate and duration of response, as well as progression-free survival and overall survival.

This example illustrates the use of existing data to accelerate drug development. There are many exciting agents, and it will be difficult to develop randomized studies for all of them. It is possible to use existing data, such as that for single-agent lenalidomide, for comparison with the doublet to show that the combination is better. Moving forward, there will be more approvals using this approach. The approval of tafasitamab-cxix plus lenalidomide provides proof of concept that it is possible to use real-world data to move drugs to patients faster and more efficiently.

Another development pertains to clinical trials in the frontline setting, such as PHOENIX, ROBUST, and the US Intergroup E1412 trial, which have provided important insights into treatment. Results from the ROBUST and E1412 trials were recently published in the *Journal of Clinical Oncology*. As I mentioned previously, treatment in the frontline setting has remained unchanged for many years. There were some design issues that possibly affected the results of these trials. The ROBUST and E1412 studies evaluated the addition of lenalidomide to R-CHOP, a regimen known as R2-CHOP. E1412 was a phase 2 trial with a simple design. Patients could be enrolled into the study upon diagnosis. Half of the patients received lenalidomide plus R-CHOP, and the other half received R-CHOP. This study was the first randomized trial to show a benefit in adding a new agent to R-CHOP. However, the study did not lead to the approval of lenalidomide in this setting because of results from the ROBUST study. The global ROBUST study was much larger and more sophisticated than E1412. The ROBUST trial used a real-world biomarker to identify patients with the ABC subtype of DLBCL who were at high risk for relapse. The trial used real-time central pathology review and real-time gene expression profiling using the NanoString platform to identify patients with ABC DLBCL at multiple centers throughout the world, with centralized laboratories in the United States, Europe, and Asia. One may say that the trial was a marvel of organization and scientific design.

However, unlike the E1412 study, the ROBUST trial did not show an improvement with the addition of lenalidomide to R-CHOP. There were some differences between the studies. The ROBUST trial was open to patients with the ABC subtype of DLBCL, whereas E1412 enrolled all comers. The dose of lenalidomide was lower in ROBUST than in E1412. However, we believe that the main reason for the difference in outcomes was differences in the study populations. The complexity of the ROBUST trial made some doctors hesitant to enroll sicker patients. For example, if a patient has disease that is rapidly progressing, the inclination is to initiate standard treatment. Patients with more stable disease—who could wait for treatment—were more likely to be enrolled in ROBUST, which resulted in a long time from diagnosis to treatment and in the accrual of lower-risk patients. This resulted in better-than-expected outcomes in the control arm of the study. In contrast, patients enrolled into the E1412 trial were able to start treatment immediately;

hence, more high-risk patients with rapidly progressing disease entered the study. These patients benefited from the addition of lenalidomide, which resulted in improved outcomes vs R-CHOP alone. Based on the comparative analysis of these trials, and our previous work demonstrating the prognostic importance of time from diagnosis to treatment, moving forward, modern studies in the frontline setting are focusing on the accrual of sicker patients with rapidly progressive and/or high-risk disease and are minimizing the time from diagnosis to treatment.

H&O Are there any other emerging treatments of interest?

GN There are several targeted therapies focused on specific molecular pathways that are being developed in this setting. This approach is currently overshadowed by the molecular subtype agnostic therapies just discussed; however, it is still very promising, particularly when treatment is combined with modern molecular profiling and "molecular clustering" of DLBCL. There is more to come in this space.

H&O Do you have any other recommendations for the treatment of these patients?

GN In the frontline setting, there are several new, exciting clinical studies with improved designs. I encourage clinicians to consider clinical trials for patients, including those with rapidly progressive disease, instead of standard R-CHOP. These patients have the most to gain from enrollment in a frontline clinical trial. Most of the studies permit the use of corticosteroids or other treatments to stabilize the patient.

In the relapsed/refractory setting, there are several new agents, as well as others in development. Typically, these patients are considered for CAR T-cell therapy first. Patients with rapidly progressive disease sometimes require bridging therapy; the doublet of polatuzumab vedotin-piiq plus rituximab and the triplet of polatuzumab vedotin-piiq, brentuximab vedotin (Adcetris, Seagen), and bendamustine are frequently used in this setting. Patients in the second-line setting who are not candidates for high-dose chemotherapy or CAR T-cell therapy are frequently treated with tafasitamab-cxix and lenalidomide. There is some evidence that when performance status improves or other factors change, these patients may benefit from subsequent treatment with CAR T-cell therapy, even drugs that target the same surface molecule (CD19). For patients who prefer oral therapy, selinexor is a new option.

The choice of treatment in this setting is complex because it depends on several factors, such as the patient's previous treatment-related toxicities, line of therapy, performance status, and organ function. The best next line of therapy will be based on the clinical scenario, the rapidity of disease progression, and toxicities from previous therapies (some of which are residual).

One of the most important areas for future research will be to understand the ideal sequencing of these therapies, particularly if more agents are coming. Real-world studies will provide important information regarding outcome and toxicity. It is unlikely that randomized studies will be able to compare different sequences of therapy.

Disclosure

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Suggested Readings

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