Immunotherapies for Pediatric B-Cell Acute Lymphoblastic Leukemia Patients

BY RICHARD SIMONEAUX

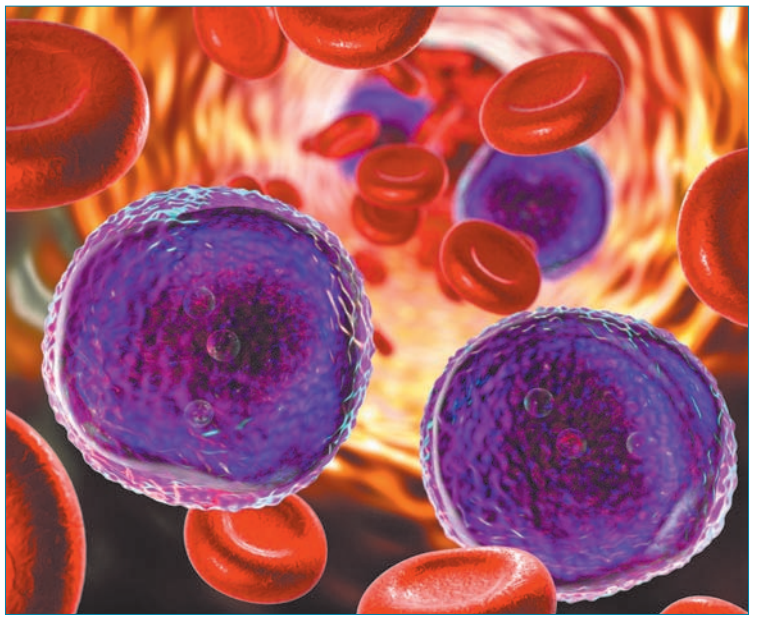
CME/CNE Article

The leading cause of death due to disease in children is cancer and, among these malignancies, leukemias account for one-third of the cases. Pediatric acute lymphoblastic leukemia (ALL), which accounts for roughly 70 percent of all pediatric leukemia cases, is divided into two distinct subtypes—precursor B-cell ALL (B-ALL) and T-cell ALL (T-ALL).

Many advances over the past decades have dramatically improved the outcomes for pediatric B-ALL patients. Nonetheless, there remains a small but significant number of patients who relapse and become resistant to traditional chemotherapy approaches. A new advance that offers hope for these more challenging cases is the development of immuno-based therapy for this patient population.

Recently, a review was published on the most relevant immunotherapies utilized for pediatric B-ALL patients (*Hum Immuno* 2019; https://doi.org/10.1016/j.humimm.2019.01.011). One of the authors of this publication is Richard Bram, MD, PhD, Chair of the Division of Pediatric Hematology/Oncology at the Mayo Clinic.

When asked about FDA-approved therapies for pediatric B-ALL patients, Bram replied, "Currently, there are just a few immunotherapies approved by the FDA for children with B-ALL, including blinatumomab, which is a bispecific antibody that targets CD3 on T cells and brings them into close contact with B cells by also binding to CD19.



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"A second FDA-approved immunotherapy is tisagenlecleucel, which is a CD19-targeted CAR T-cell therapy. Although other companies are also generating CD19 specific CAR-T cells for use in pediatric B-ALL, they are not yet FDA-approved in that population."

Although the outcomes for pediatric B-ALL patients have dramatically improved over the last few decades, a subset of these patients continue to have poor prognoses based on the risk factors present in their disease.

In the classic NCI risk-stratification system, patients are classified as NCI standard risk if at diagnosis their peripheral white blood cell count is less than 50,000 per microliter and they are between 1 and 9 years old; all other patients not meeting these criteria are classified as NCI high-risk. More modern risk-stratification systems employ a variety of different prognostic factors, including the presence of high- or low-risk cellular abnormalities, as well as early induction therapy response, including the presence of minimal residual disease (MRD).

The most prominent modern therapeutic approach for de novo high-risk ALL patients is to use enhanced strength chemotherapy. For some specific high-risk subgroups, such as patients having Philadelphia chromosome-positive (Ph+) ALL, the use of additional targeted therapies (e.g., tyrosine kinase inhibitors) may prove beneficial. At some clinics, the use of hematopoietic stem cell transplantation (HSCT) is also considered after remission for certain very high-risk subgroups, especially if the patient has a suitable matched related donor.

Patients with relapsed and refractory B-ALL present a unique challenge for clinicians. Despite the use of augmented chemotherapy and stem cell transplantation, many patients' long-term treatment will be characterized by relapse or disease progression. Consequently, the development of novel therapeutic agents is direly needed to improve the long-term survival in this patient population. Thus, novel immunotherapies are more frequently being incorporated into effective treatment strategies in the relapsed and refractory B-ALL setting.

Hematopoietic Stem Cell Transplantation

For pediatric B-ALL patients with high-risk disease, including those that are relapsed, refractory, or have specific high-risk features, HSCT is the accepted standard of care.

Currently, most pediatric HSCT employs supralethal (i.e., myeloablative) conditioning regimens. However, for older and heavily pretreated patients, there has been increased interest in the development of milder protocols. Frequently, myeloablative conditioning for B-ALL will consist of several daily fractions of total body radiation, combined with high doses of IV chemotherapeutic agents (e.g., etoposide, cyclophosphamide, or fludarabine).

Improvements in supportive care have reduced the risks for death and treatment-related toxicities, such as sinusoidal obstruction syndrome. Hematopoietic stem cells can be isolated either from the donor's bone marrow or via leukapheresis from their peripheral circulating mononuclear cells after mobilization from the bone marrow following treatment with granulocyte-colony stimulating factor. Once patients are infused with the stem cells, dosing with immunosuppressive agents is initiated to reduce the chances of graft-versus-host disease (GVHD).

The relatively limited availability of HLA-matched donors is a critical issue for HSCT, as only roughly 30 percent of candidates have a matched sibling. As a result, it has been necessary to greatly expand the use of unrelated donors; this has been greatly facilitated by the success of the National Marrow Donor Program.

A major advance for donor HSCT arose from the observation that, shortly following donor stem cell infusion, alloreactive T cells can be selectively eradicated by treatment with cyclophosphamide due to their rapid activation and replication rates. As a result, quiescent hematopoietic stem cells, which divide slowly and have an enhanced ability to metabolically inactivate the drug, are spared. This has allowed expanded use of HSCT for children, as parents can frequently serve as a stem cell donor.

Antibody-Drug Conjugates

Antibody-drug conjugates, like monoclonal antibodies, are able to selectively target tumor cells based on the proteins expressed on their surface. They target tumor cells by having an antigen-binding domain, which binds surface-bound proteins present on tumor cells. However, instead of antibody-dependent cytotoxicity, these products

Continued on page 16

continued from page 15

primarily work by selective delivery of a cytotoxic drug to malignant cells, thereby leading to targeted cell death. Some examples of these hybrid therapies include the anti-CD33/calicheamicin conjugate gemtuzumab ozogamicin, the anti-CD30/monomethyl auristatin E conjugate brentuximab vedotin, and the anti-CD22/calicheamicin conjugate inotuzumab ozogamicin.

The FDA approved inotuzumab ozogamicin in August 2017 for the treatment of adults with relapsed/refractory B-ALL based on the results obtained in a phase III trial (NCT01564784) that demonstrated higher rates of remission than standard chemotherapy. The use of this conjugate in children with CD22-positive relapsed or refractory B-ALL was explored in a phase II study by Children's Oncology Group (AALL1621, NCT02981628).

"Although the study is still under way and preliminary study results have not been publicly released, off-label use, despite the lack of FDA approval, has been reported in approximately 100 pediatric patients treated under the FDA's expanded access 'compassionate use' program (NCT03127605)," Bram noted.

Bispecific T-Cell Engagers

For patients with B-ALL, blinatumomab is a relevant example of a bispecific T-cell engager. The structure of this antibody consists of a fusion protein that combines the VL and VH regions of monoclonal antibodies that show specificity for the extracellular portions of CD19 (which is overexpressed on malignant B cells) and CD3 (present on T cells). Mechanistically, this therapy is thought to initiate T-cell receptor-mediated activation and killing of the targeted cells by binding to both the CD3 on the surface of T cells and CD19-positive B-precursor ALL cells.

In December 2014, the FDA granted accelerated approval to blinatumomab for Philadelphia chromosome-negative (Ph-) relapsed or refractory B-ALL. This approval was based upon the results obtained in a single-arm phase II study (NCT01466179) conducted in adults with relapsed or refractory Ph- B-ALL. As is necessary in the accelerated approval program, clinical benefit was subsequently confirmed in the randomized TOWER trial (NCT02013167), which led to regular approval by the FDA in July 2017. At that time, in addition to regular approval, the permitted use of blinatumomab was expanded to include patients with relapsed or refractory Ph+ B-ALL. This added indication was based on results from the ALCANTARA trial (NCT02000427), which demonstrated efficacy in Ph+ B-ALL patients who showed resistance or intolerance to tyrosine kinase inhibitors.

In March 2018, the FDA expanded the use of blinatumomab to include treatment of pediatric and adult B-ALL patients in first or second remission but with MRD of ≥ 0.1 percent; this decision was based on results obtained in the BLAST trial (NCT01207388). In a phase I/II study (NCT01471782) among children with B-cell precursor ALL, blinatumomab showed complete MRD response in that patient population (*J Clin Oncol* 2016:34;4381-4389).

CAR T Cells

Chimeric antigen receptor (CAR) T cells are produced from a patient's own T cells. In this protocol, a patient's CD3+ T cells are first isolated via leukapheresis and then sent to a clinical laboratory for modification. Ex vivo, the cells are transduced using a lentiviral vector to code for a CAR that targets the protein CD19. After this modification, the T cells then undergo an expansion, are cryopreserved, and returned to the patient's local clinic for infusion.

CARS for the two clinically approved CAR-T therapies, axicabtagene ciloleucel (KTE-C19) and tisagenlecleucel (CTL019), comprise an extracellular single-chain variable fragment connected to one or more intracellular signaling domains. These domains activate the T-cell based proliferation and cytotoxicity upon recognition of the target antigen in a major histocompatibility complex (MHC)-independent manner.

Continued on page 17

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Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Describe current therapies for pediatric B-ALL patients. 2. Identify several therapies being investigated in ongoing clinical studies pediatric B-ALL patients.

Disclosure: The author has disclosed that the U.S. Food and Drug Administration has not approved the use of inotuzumab for pediatric patients with relapsed refractory B-ALL as noted in this article. Please consult the product's labeling for approved information.

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continued from page 16

"This mechanism allows CAR-T cells to specifically target tumor cells expressing a certain antigen in a manner that is MHC-independent, which is important, as tumor cells often downregulate MHC class I," Bram explained.

In August 2017, the FDA approved the CAR-T therapy tisagenlecleucel for the treatment of pediatric refractory B-ALL patients, as well as those with relapsed disease after failure of first-line salvage therapy. Simultaneous with this approval of tisagenlecleucel, the FDA also approved the use of the monoclonal antibody tocilizumab for patients undergoing CAR-T therapy greater than 1 year of age that develop the potentially fatal cytokine release syndrome. In May 2018, the FDA approved the expanded use of tisagenlecleucel to adult relapsed/refractory large B-cell lymphoma patients.

In October 2017, the CD19-targeting axicabtagene ciloleucel was approved by the FDA for the treatment of relapsed or refractory large B-cell lymphoma in adults. In the ongoing single-arm phase I/II ZUMA-4 study (NCT02625480), the safety and efficacy of axicabtagene ciloleucel is being evaluated in pediatric patients with refractory/relapsed B-ALL after at least one salvage therapy or relapsed after HSCT (*J Clin Oncol* 2016;34(15_suppl):TPS7075-TPS7075). Patients in this study will receive fludarabine and cyclophosphamide-based conditioning, and subsequently, 2×106 CAR-T cells per kg.

Immunotherapy Discussion

When asked about the use of non-FDA-approved therapies in this patient population, Bram stated, "we must often use drugs off-label because the FDA has not yet approved certain drugs in children at the time they are needed. One such therapy that we use in children with relapsed refractory B-ALL is inotuzumab, an anti-CD22 antibody-drug conjugate, which is FDA-approved for use in adults but not yet approved in children. I believe it is likely that the FDA will approve it in the near future, if it continues to have good outcomes in clinical studies."

Bram also discussed the therapies being investigated in ongoing clinical studies. "Inotuzumab is one that is currently being studied. Other studies are using axicabtagene ciloleucel, a CD19-targeted CAR-T therapy; there are some interesting differences in the various details of the CAR-T cells made by different companies. These details

Continued on page 18

A Conversation With Susan Rheingold, MD, About B-Cell Acute Lymphoblastic Leukemia


SUSAN RHEINGOLD, MD

In a recent interview with *Oncology Times*, Susan Rheingold, MD, of the Children's Hospital of Philadelphia, discussed some of the treatment options for pediatric patients with B-cell acute lymphoblastic leukemia (B-ALL).

What are the most common immunotherapies you utilize in your clinical treatment of pediatric B-ALL patients?

Currently, immunotherapy is used at relapse, although the Children's Oncology Group (COG) is asking whether blinatumomab, inotuzumab, and CAR-T immunotherapy (CTL019) can be brought forward to newly diagnosed children. At first relapse, we are investigating blinatumomab + chemotherapy and at second relapse inotuzumab monotherapy. Both of these drugs are in common use for relapse, although only blinatumomab is FDA-approved for pediatric relapse. More rarely in use is rituximab. Daratumumab is now being tested in phase I trials for children. In addition, new bispecific antibodies are under development.

What are the strengths and limitations of the immunotherapies you've mentioned?

At relapse, about one-third of children will respond to blinatumomab but more patients seem to respond when disease burden is lower (MRD low studies in adults). Blinatumomab is a 28-day continuous infusion, so it requires a child to wear an infusion backpack to be given continuously. It has many of the same side effects initially as CAR-T therapy with cytokine release syndrome and neurotoxicity being the most significant.

Inotuzumab had about 66 percent response rate in a retrospective analysis of compassionate use in pediatric patients. It is given once a week IV for 3 weeks and is generally very well-tolerated, but it does affect the liver. And in children who undergo a bone marrow transplant post inotuzumab-induced remission, there appears to be an increased risk of sinusoidal occlusive syndrome. Both will cause a temporary B-cell aplasia and can cause prolonged cytopenias.

What are the available treatments for pediatric B-ALL patients who undergo relapse?

Very few of the discussed therapies are currently approved in pediatrics for first relapse, but there are many studies out there right now investigating the new classes of immunotherapy and cellular therapy.

Some of the more interesting studies include the following:

- AALL1331 COG trial (NCT02101853)-blinatumomab randomization on a UK ALL R3 backbone;
- inotuzumab investigational studies (AALL1621, NCT02981628);
- CAR T-cell 19 (NCT03467256) and CD22 (NCT02315612) therapy trials (including the FDA-approved tisagenlecleucel);
- Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) trials looking at temsirolimus with etoposide and cyclophosphamide (T2014-001, NCT01614197), liposomal vincristine sulfate in combination with UK ALL R3 induction chemotherapy (T2012-002, NCT02879643), and ixazomib in combination with chemotherapy (T2017-002, NCT03817320);
- carfolizimib (NCT02303821); and
- pharmaceutical sponsored trials such as daratumumab.

In addition, new targeted therapies are being matched to genetic and molecular abnormalities which seem to be discovered on almost a monthly basis in leukemia.

What are some of the challenges in your treatment of pediatric B-ALL patients?

Standard risk ALL has a 95-98 percent cure rate, which is hard to beat. The toxicity of combined chemotherapy has also been mitigated to minimize late effects. However, other subsets of ALL, including infant KMT2A rearranged ALL, Philadelphia-like ALL, and hypodiploid ALL have much worse outcomes and are our biggest challenges. Designing trials that allow these patients access to newer immune-based or targeted therapies is a priority for pediatric oncologists.

What do you see as future directions for pediatric B-ALL therapy?

Each new diagnosis will have their leukemia interrogated to assess for targeted therapy and immunotherapy options that will come into play much sooner. For some of the patients with poor outcomes, moving up immunotherapy earlier and not waiting for relapse will lead to decreased need for bone marrow transplant due to fewer relapses and more alternative cellular therapies. OT

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continued from page 17

may affect the longevity of the treatments, so it will be very interesting to compare outcomes and see which work the best."

When queried about the mechanisms by which B-ALL can become treatment-resistant, he stated, "Resistance can develop following immunotherapy that targets a single molecule (typically CD19). One of the main ways that resistance develops is if an offshoot of the leukemia cells loses expression of the target protein. Thus, it is important in relapses after blinatumomab or CAR T-cell therapy to check the leukemia cells for surface expression of CD19.

"In many of these cases, the CD19 protein is gone, and then it becomes important to try to target a different protein, such as CD22," he explained. "In rare cases, the CD19 protein is not completely gone, but simply mutated to delete the small part of the protein that is recognized by the immunotherapy antibody or CAR receptor."

In noting some methods being employed to circumvent disease resistance development, Bram noted, "Some investigators are currently testing dual targeting (both CD19 and CD22) at the same time, to see if that can prevent resistance from developing. Fortunately, the majority of children with B-ALL seem to be responding well and only a minority seem to be developing resistance. More studies will need to be done to determine the long-term outlook."

Bram pointed out the differences between treating children versus adult B-ALL patients. "Pediatric immunotherapies use generally the same approach as those used for adults; however, FDA approval does not always come for both populations at the same time. Additionally, some seem to work better in older or younger patients, depending upon the disease subtype and the therapy. It is not always clear why there is this age difference in effectiveness, but it may have to do with the general changes in the immune system that happen as we get older (i.e., less able to mount an immune response)."

When asked how the therapies for T-ALL differ from those for B-ALL, Bram explained, "Treatment for T-ALL is completely different, and unfortunately we do not yet have a good immunotherapy for T-ALL. With respect to CAR-T therapy, the problem is that T cells themselves are the 'leukemia killers' and so if they would be programmed to kill T-ALL cells, they would also just kill themselves.

"In addition, humans cannot live long-term without T cells because that causes severe combined immunodeficiency. Consequently, an immunotherapy that attacks T-ALL will be very immunosuppressive, as it will most likely kill normal T cells in the immune system. However, there are more complicated approaches that might work in the future, including generating resistant T cells that could still kill T-ALL cells but not be destroyed themselves.

"Future directions for pediatric B-ALL," he continued, "include finding and testing more targets (such as CD22) so that resistance can be avoided. Additionally, various ways to increase the survival and proliferation of CAR-T cells in the body are being actively explored.

"For instance, it may be useful to combine CAR-T or monoclonal antibody therapy with checkpoint inhibitors, such as anti-PD1. PD1 acts as a set of brakes on the immune system, and antibodies that block it have already been shown to be helpful in certain types of cancer immunotherapy such as for melanoma. It may be that blocking PD1 would also help immunotherapy for B-ALL work better in the future.

"Additional approaches might be to alter the CAR-T cells using genetic engineering with CRISPR/Cas9 technology to increase their survivability by knocking out 'death' pathway proteins," Bram concluded. OT

Richard Simoneaux is a contributing writer.