

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## New Approaches to T-Cell Acute Lymphoblastic Leukemia



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### **H&O** How common is T-cell acute lymphoblastic leukemia (T-ALL)?

**DT** ALL is uncommon, accounting for approximately 6700 new diagnoses per year in the United States. Between 75% and 85% of these cases are B-cell ALL, which means that T-cell ALL develops in fewer than 2000 people in the United States—both adults and children—each year. Although ALL is the most common cancer in children, childhood cancer is rare, with an incidence of approximately 10,000 to 15,000 per year in the United States—just a small fraction of the pie in comparison with the more than a million new cases of adult cancers each year.

### **H&O** Who is most likely to be affected?

**DT** ALL is primarily a disease of children, with T-ALL tending to affect older children, adolescents, and young adults. T-ALL usually presents in children between the ages of 8 and 18 years, but it is also seen in younger children and in adults. Of note, T-ALL is 2 to 3 times more common in males than in females, and it also disproportionately affects Black children.

### **H&O** What is the standard first-line treatment in T-ALL?

**DT** The standard first-line treatment in children and young adults is multiagent chemotherapy with regimens first developed in the 1960s. ALL was incurable 70 years ago, but today most people are cured. Outcomes for

T-ALL were historically worse than those for B-ALL; however, with modern therapy, survival is similar.

The total duration of therapy for T-ALL is 2½ to 3½ years. Treatment starts with 6 to 8 months of chemotherapy that is broken down into cycles. Although this initial phase of therapy is the most intensive, it is given primarily on an outpatient basis. Patients still need frequent visits to the clinic, however, and sometimes must be hospitalized for complications of therapy. After the initial cycles of more-intensive chemotherapy, patients transition to low-intensity maintenance chemotherapy, which requires them to take medicines daily at home and visit the clinic once a month. Over the course of treatment, patients are treated with more than 10 different medications, some of which are taken by mouth; others are administered intravenously, and still others intrathecally (such as by lumbar puncture). Almost all these medications were first identified and then approved by the US Food and Drug Administration (FDA) in the 1950s, 1960s, and 1970s. Historically, boys received an additional year of therapy because of the risk for testicular relapse with the less-intensive protocols used in the 1960s and 1970s. With modern therapy, however, this extra year has been largely abandoned by most cooperative groups and centers. The improved outcomes for T-ALL arose from carefully designed, rigorous cooperative group clinical trials around the globe. Although there are differences in the backbones used, the regimens are similar across North America, Europe, and Asia. The treatments used in developing countries, where access to care is more difficult, are different. Even though most of the drugs used are relatively old, some of them remain quite expensive.

A key part of therapy is central nervous system (CNS) prophylaxis. Historically, this was achieved with a combination of intrathecal chemotherapy, CNS-directed systemic therapy, and cranial radiation. We have recently found that most children with T-ALL can be cured without cranial radiation, which is a huge advance.

### **H&O** Could you discuss the findings of recent studies?

**DT** Cure rates have reached the point where they are today through clinical trials conducted by multiple international cooperative groups. I will focus on 2 recently completed trials from the Children's Oncology Group (COG). AALL0434, which was published in 2020, was a phase 3 trial of more than 1500 children and young adults with T-ALL and T-cell lymphoblastic lymphoma (T-LL). This trial included 2 randomizations. First, patients were randomly assigned either to escalating-dose methotrexate without leucovorin rescue plus pegaspargase (Oncaspar, Shire), or to high-dose methotrexate with leucovorin rescue. Second, intermediate- and high-risk patients were randomly assigned to receive or not receive six 5-day courses of nelarabine. The study found that escalating-dose methotrexate was superior to high-dose methotrexate, which was unexpected at the time. The study also showed that the addition of nelarabine improved disease-free survival.

AALL1231, which we published in early 2022, was a phase 3 trial of more than 800 children and young adults with T-ALL or T-LL. Patients were randomly assigned to a modified augmented Berlin-Frankfurt-Münster (BFM) chemotherapy regimen with or without bortezomib during 2 blocks of therapy. This trial also made changes to the backbone to eliminate cranial radiation in most of the children with T-ALL. Corticosteroids were changed from prednisone to dexamethasone throughout therapy, and 2 extra doses of pegaspargase were added. More than 90% of patients with T-ALL in AALL0434 received cranial radiation, and we hoped to avoid that.

We found that bortezomib improved event-free survival and overall survival in the participants with T-LL, but not in those with T-ALL. This was completely unexpected. Over the past 30 years, therapy has been harmonized for T-ALL and T-LL because they are considered a spectrum of the same disease. We want to understand why that difference between the 2 groups occurred. Ongoing research funded by the National Institutes of Health (NIH) is exploring the difference.

We were also successful at eliminating cranial radiation in most of the children with T-ALL. A comparison of patients in AALL0434 who received cranial radiation with similar patients in AALL1231 who did not receive cranial

radiation demonstrated similar outcomes. In AALL1231, fewer than 10% of patients received cranial radiation.

### **H&O** What are the shortcomings of standard first-line treatment for T-ALL?

**DT** First, the treatment is lengthy, lasting for several years. That is a concern from an access-to-care standpoint, especially for patients with limited means. The current therapy has risks for both short- and long-term side effects. The effects of years of chemotherapy are magnified by the fact that the patients are usually young, which means that their brains and bodies are still developing. Now that children who were treated in the late 1970s and early 1980s are in their 50s and 60s, we are seeing the long-term effects of that therapy. We do know that childhood cancer survivors as a group tend to be at increased risk for heart attacks, strokes, diabetes, hypertension, and secondary malignancies.

A major difference between the early 1980s and now is that most children used to receive cranial radiation as part of their treatment. We hope that the results of AALL1231 will reduce the number of children who receive cranial radiation, with fewer long-term consequences of this treatment. That said, patients are looking at multiple years of chemotherapy.

The other major problem besides duration of treatment and side effects is that we still are not curing everybody. Although the cure rate for T-ALL is now approximately 85% to 90%, that still leaves approximately 10% to 15% without a cure. Unfortunately, cure rates for children whose T-ALL recurs are very low—less than 30%. We approach T-ALL knowing that we really have only one good shot at cure, so we need to use our most effective medicines in frontline treatment.

### **H&O** Are certain patients more likely to benefit from treatment?

**DT** Unfortunately, we are not very good at identifying which patients with T-ALL are more likely or less likely to be cured. In those with B-ALL, factors such as age at presentation, white blood cell count at diagnosis, and tumor biology are highly important in risk stratification. In T-ALL, the only marker that is independently prognostic and has been validated in multiple studies is response to therapy. We evaluate patients with bone marrow aspiration and biopsy approximately 30 days after the initiation of treatment, and we use morphology and minimal residual disease (MRD) assessment for risk stratification. For those who have persistent disease after 1 month on the basis of either morphology or MRD positivity, we repeat the bone marrow aspiration 2 months later. Patients who

are in morphologic remission and are MRD-negative after that first month have a significantly better chance of being cured, whereas those who have detectable disease after 3 months have a significantly lower chance of being cured.

We do have an exciting correlative study funded through the NIH Gabriella Miller Kids First Pediatric Research Program, which involves comprehensive genomic profiling in more than 1300 children with T-ALL. This large genomic effort represents a collaboration between COG and St. Jude Children's Research Hospital. We are cautiously optimistic that we will be able to identify prognostic biological markers in T-ALL blasts. We anticipate publication of the initial results of that effort this year.

## Another very active area for research in treating patients with relapsed T-ALL is immunotherapy.

### H&O Is there some suggestion that children with *NOTCH1* mutations do better?

**DT** Data from Europe do show a correlation between *NOTCH1* mutations and better outcomes, but the relationship does not hold up once you factor in MRD. Part of the problem we are encountering with identifying specific gene mutations that predict outcomes is that in T-ALL, a lot of the important leukemic drivers are in noncoding parts of the genome. That is, in many cases, the mutations that drive the leukemia may not be in the gene itself, but in something else that regulates that gene. So instead of looking for changes in genes, we need to look at the many different ways in which an oncogene can be activated.

### H&O What treatments are available to patients whose disease recurs after initial treatment?

**DT** Multiple drugs for recurrent T-ALL are currently in early-phase trials in the United States. Several trials are looking at the use of small-molecule inhibitors such as ruxolitinib (Jakafi, Incyte), which targets the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway; venetoclax (Venclexta, AbbVie), which targets the B-cell lymphoma 2 (Bcl-2)

protein; and palbociclib (Ibrance, Pfizer), which targets cyclin-dependent kinase 4 (CDK4) and CDK6.

Ruxolitinib is being looked at in early-phase trials in different types of leukemia. Preclinical studies suggest that certain types of T-ALL, including early T-cell precursor ALL, are more likely to benefit from JAK-STAT inhibitors. One trial of particular interest is being conducted at St. Jude, where ruxolitinib is being used in the front line for certain patients with T-ALL (NCT03117751).

In a phase 1 trial that was published in 2021, Pullarkat and colleagues found that the addition of venetoclax to low-dose navitoclax and chemotherapy had promising efficacy in 47 patients—most of them adults—with relapsed or refractory ALL or lymphoblastic lymphoma, and the regimen was well tolerated. On the basis of these exciting results, COG is developing an early-phase trial, but it is very early in development.

In addition, a recently completed phase 1 study from COG examined the use of palbociclib with chemotherapy in pediatric and young adult patients who had relapsed or refractory ALL or lymphoblastic lymphoma. Preliminary results that Dr Elizabeth Raetz presented at the 2020 American Society of Hematology (ASH) Annual Meeting suggested that the combination is safe and well tolerated.

Another very active area for research in treating patients with relapsed T-ALL is immunotherapy. Several immunotherapies have shown remarkable promise in B-ALL, including chimeric antigen receptor (CAR) T cells, bispecific antibodies, and monoclonal antibodies. Indeed, 3 different immunotherapies were approved by the FDA for B-ALL in 2017. Immunotherapies target both malignant and nonmalignant cells that contain the surface antigen of interest; B-cell cancers are a good choice to target because the risks of depleting normal B cells are manageable. In contrast, we must be very careful about the consequences of targeting normal T cells in patients with T-cell malignancies.

My research laboratory investigated the use of daratumumab (Darzalex, Janssen Biotech), a monoclonal antibody that is approved to treat patients with multiple myeloma, in preclinical models of T-ALL. Daratumumab was surprisingly effective in mouse models of immunodeficiency. Typically, naked monoclonal antibodies are not effective in these models. This work has been validated by several research laboratories. The research led to a phase 2 clinical trial, sponsored by Janssen, in patients with relapsed or refractory ALL (NCT03384654); results will be presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. We are hoping to move daratumumab into the front line in future cooperative group trials.

The other exciting advance in immunotherapy is the use of CAR T cells. Preclinical data on CAR T cells in

relapsed T-ALL are very exciting, and we are starting to see published clinical results, most of them from China, that are very promising. An especially interesting trial by Pan and colleagues appeared in the *Journal of Clinical Oncology* in 2021. In this phase 1 trial, CD7 CAR T-cell treatment produced a high rate of complete remission in 20 patients with relapsed or refractory T-ALL; 15 patients were in complete remission after a median follow-up of 6 months. A phase 2 trial from Beijing is following up on these results (NCT04689659).

A few trials of CAR T-cell therapy for T-ALL have opened in the United States, and we will see many more open this year. At our center, we hope to open a trial later this year to investigate an autologous CAR T-cell therapy that targets CD38. This CAR T-cell therapy was developed as a collaborative effort between the laboratories at the University of Pennsylvania and those at the Children's Hospital of Philadelphia, with generous research support from the Leukemia and Lymphoma Society. The potentially exciting thing about targeting CD38 is that CD38 is highly expressed not only in T-ALL and T-LL but also in acute myeloid leukemia and multiple myeloma. We also have an ongoing collaboration with Beam Therapeutics to develop an "off-the-shelf," gene-edited, CD7-directed CAR T-cell therapy. Preclinical data on both these CAR T-cell therapies will be published in 2022.

Overall, it is difficult to conduct trials in relapsed/refractory T-ALL because of the few patients available. T-ALL is rare to begin with, and recurrence develops in only 15% to 25% of patients. Patients are often very ill when they have a relapse, making travel difficult. To advance the science and develop new treatments, we cannot open trials just at single centers.

### H&O What should be the next steps in research?

**DT** It is an exciting time in T-ALL research, both in the clinic and in the laboratory, and we have several goals.

First, we want to be able to predict which children with T-ALL and T-LL are going to do better or worse. Thus, we really need to understand the biology of the disease better. Second, we need to understand the biological differences between T-ALL and T-LL. Third, we need to continue preclinical studies with the goal of developing better novel therapies, especially CAR T-cell therapies and other immunotherapies, and translate them into the clinic.

### Disclosure

*Dr Teachey serves or has served in the past 2 years on advisory boards for Sobi, Beam Therapeutics, and Janssen. His research laboratory has received funding from Beam Therapeutics and NeoImmune Tech.*

### Suggested Readings

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