Review of Evolving Treatment Approaches in Pediatric Patients with Newly Diagnosed AML

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Program Overview
Managing AML recently interviewed Richard Aplenc, MD, PhD, MSCE, a Professor of Pediatrics at Children's Hospital of Philadelphia. In this activity, Dr. Aplenc explains how we might tailor therapies to pediatric patients and how new therapies may improve treatment outcomes.

How common is pediatric AML?

Acute myeloid leukemia (AML) is the second most common blood cancer in children behind acute lymphocytic leukemia (ALL). It comprises about 20% to 25% of all blood cancers in children. About 500 children a year in the United States under the age of 14 are diagnosed with AML.

How has the treatment paradigm evolved for these young patients in recent years?

Very early on, ALL and AML were treated the same, but it became clear that treatments effective for ALL were not effective for AML. In the 1980s, we began to move towards intensified chemotherapy and focus on two groups of medications, cytarabine and anthracyclines. Now in the United States and across the world, the chemotherapy backbone for AML contains cytarabine and anthracyclines. The current treatment paradigm has been stable since the early 2000s in terms of those medications and how they are combined—approximately 80% of children in the US have been treated with a very similar chemotherapy backbone over the past few decades.

Since then, outcomes have improved modestly, in part due to the use of gemtuzumab ozogamicin, an anti-CD33 monoclonal antibody, and now with the use of multikinase inhibitor sorafenib for certain patients with *FLT3* internal tandem duplication (*FLT3*-ITD). In general, we are focused on identifying specific molecular subtypes of AML, such as *FLT3*-ITD, that may respond to therapies tailored to those subtypes.

We've also become much better over the past 20 years in managing the infectious complications of chemotherapy. And recently, we have a greater awareness of the need to more effectively manage the cardiac complications related to anthracyclines, including daunorubicin, which is the one we use most, as well as mitoxantrone. There's now data to show there are children whose survival is impacted by anthracycline-associated heart damage.

The role of stem cell transplantation also has changed over the past 20 years. We're transplanting many more children now than we did before. There is data that this approach is beneficial for some patients, but it's also not clear that all pediatric AML subtypes benefit from stem cell transplant. I think that is one of the most important clinical research questions facing us today in pediatric AML.

What is the role of induction therapy in patients with pediatric AML?

The primary goal of induction is two-fold: one is to make the leukemia go away as much as possible, and the other is to identify patients who are unlikely to be cured with standard chemotherapy, for whom transplant may be beneficial. Induction also gives us time to complete the molecular testing needed to characterize the leukemia. That testing may take 3-4 weeks to complete.

Induction chemotherapy is the best test of whether the leukemia is going to be sensitive to chemotherapy. If after two rounds of AML induction there's still leukemia, that is good evidence that the leukemia is fairly chemotherapy resistant, at least to anthracycline-based therapies. Based largely on induction response, we decide which patients to take to stem cell transplant. We only take some patients to transplant, because transplant has more side effects than AML chemotherapy, and there's a higher chance of dying during transplant than in any one AML chemotherapy course. It's not something that you would give every patient if you had a less toxic alternative with equal efficacy.

Should all children with newly diagnosed AML be enrolled clinical trials, ideally?

Yes, that's the approach we take in pediatric oncology in general. We only learn how to improve treatments for treating pediatric AML patients in the context of a clinical trial, for a couple of reasons. The first is that there are only 500 children a year in the country with AML. From a statistical standpoint, you won't have a reasonable chance at understanding whether a therapy makes a difference or not without a large sample size. You can only get a large number of patients if you're doing a study that's open in many centers, and that can only happen in the context of a clinical trial. That's really a fundamental component to the culture of pediatric oncology. Of course, we would never force anybody into a clinical trial and always want patients and their families to fully understand what they're agreeing to when they join a clinical trial.

What novel therapies have shown the most promise in the treatment of pediatric AML?

I mentioned tailoring therapies to specific molecular subtypes. A great example of that is tyrosine kinase inhibitors targeting the *FLT3* protein, which is often mutated or altered in adult and pediatric AML. There are a number of medications in that class. The two that are used the most in pediatrics are sorafenib, which we studied as part of a Children's Oncology Group (COG) trial, and that data was just recently published, and another is gilteritinib, which is being studied now in AAML1831, a current phase 3 trial in the COG. In this study, standard chemotherapy is being compared to therapy with CPX-351 and/or gilteritinib in newly diagnosed AML patients with or without *FLT3* mutations.[1]

The sorafenib data indicates that the addition of sorafenib improves outcome for patients who have what we call a high *FLT3*-ITD allelic ratio.[2] A very narrow subset of children with AML fall into that box—about 8%. Another 4% of children that have that same mutation, but in a lower amount, so a lower allelic ratio; we don't know whether sorafenib benefits them from pediatric trial data. Although ITD is the most common type of *FLT3* mutation, there are others that are point mutations in the tyrosine kinase domain (*FLT3*-TKD). We don't know yet whether gilteritinib helps improve outcomes in patients who have those point mutations. There's good data that sorafenib probably doesn't, but gilteritinib is a different subclass of the TKIs and may have benefit.

In that sense, would you also consider gemtuzumab ozogamicin to be a targeted therapy?

It's a great question, and the answer depends on how you use the word 'targeted.' It's targeted in the sense that it's targeting one specific protein, CD33, on the surface of AML cells—not all AML cells, but a very substantial majority: about 85% to 90% of pediatric AML cases are considered CD33-positive.[3] So one could say that gemtuzumab is targeted because it is directed against a particular protein on the cell surface. On the other hand, gemtuzumab targets all AML cells with CD33 on the surface rather than a specific genetic mutation. So in that way gemtuzumab differs from sorafenib and gilteritinib which are used to target *FTL3*-mutated AML.

So what does all this mean practically for the tailored treatment of pediatric patients with AML?

Currently in the Children's Oncology Group AAML1831 trial, all patients receive gemtuzumab based on prior COG data showing a decreased rate of relapse in patients treated with gemtuzumab. For patients treated off-protocol, locally we give gemtuzumab to those whose AML expresses CD33 on the cell surface. Based on a study published very recently in the *Journal of Clinical Oncology*,[2] we give sorafenib to patients with high allelic ratio *FLT3*-ITD mutations. I see the commonality in these two therapies as applying a specific medication based on molecular characterization of the patient's AML.

The COG AAML1831 phase 3 trial you mentioned is also evaluating CPX-351 as compared to standard chemotherapy as treatment for newly diagnosed AML. What is the rationale for including CPX-351 in this trial?

As I said before, cardiac toxicity is one of the main side effects of AML therapy. CPX-351 is a liposome-encapsulated formulation of daunorubicin and cytarabine. The hope is that CPX will decrease the cardiac toxicity by taking the daunorubicin and putting it essentially in these small lipid micro-containers—the idea being that we'll package the daunorubicin in a way that we'll protect the heart. The AAML1831 study is evaluating whether CPX-351 is better than the daunorubicin and cytarabine alone. CPX-351 is what we would call the primary randomization on 1831—the most important question we're asking within that study. Then we have some downstream questions that we're asking around gilteritinib in a smaller number of patients.

What data provided the rationale for evaluating CPX-351 in this setting?

CPX-351 is Food and Drug Administration (FDA)-approved for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients aged one year and older. There certainly seems to be an efficacy signal helpful for some patient adult populations.[4] The Children's Oncology Group also led a phase 1/2 trial of CPX-351 in 38 children with relapsed AML that had very good outcomes, including manageable toxicity and response rates better than what was seen in relapsed pediatric AML patients in prior North American cooperative group clinical trials.[5] These were not newly diagnosed patients and it was not a randomized comparison, but the results were very encouraging, and it's part of what led the pediatric oncology community to embrace the CPX-351 trial in COG (ie, the aforementioned AAML1831 study).

If primary results of AAML1831 are positive, what would be the implications be for the treatment of the first-line treatment of pediatric AML?

If the study shows that CPX-351 is better than standard chemotherapy with cytarabine and daunorubicin, then many centers will move to using CPX-351 as frontline therapy. There's a little bit of a complexity here in that this trial will tell us whether CPX-351 is better than daunorubicin and cytarabine, but it won't tell us whether CPX-351 is better than daunorubicin, cytarabine, and etoposide, which was the prior standard of care. So it will still be a question when this trial is done whether CPX-351 is better than what we were doing historically for these patients, and then practitioners will need to decide.

If CPX-351 is less effective than daunorubicin and cytarabine, then CPX-351 won't go forward as a frontline therapy. If there is not a difference in effectiveness, then it may or may not go forward—that will depend on whether there is more or less cardiac toxicity. If the outcomes are the same, but it has less cardiac toxicity, that would be a reason to take it forward, potentially. But if the outcomes are the same and the cardiac toxicity is worse, then it wouldn't go forward.

Thank you for your comments. Any final thoughts on the future of pediatric AML therapy?

The take-home message is that there are new therapies being developed now for pediatric AML that have the potential to improve outcomes in a substantive way. Clinical trials are the primary mechanism by which we understand whether a particular medication may help patients and to understand the side effects in children. We're going to need to continue our engagement in the clinical trial process to really understand how to use these medicines most effectively in children.

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