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Bridging the Gap in AYA Cure Rates

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You're listening to Project Ontology on ReachMD. This podcast, titled “Bridging the Gap in AYA Cure Rates,” is sponsored by Jazz Pharmaceuticals. Here’s your host, Dr Ibrahim Aldoss.

Dr Ibrahim Aldoss:
This program is intended for healthcare professionals, and I’m a paid consultant for Jazz Pharmaceuticals. My name is Dr Ibrahim Aldoss, and I’m a board-certified hematologist-oncologist specializing in acute lymphoblastic leukemia, or ALL. I’m also an associate professor in the Department of Hematology and Hematopoietic Cell Transplantation in Southern California.

I want to thank you for joining me to discuss the use of asparaginase therapy in adolescents and young adults, or AYA, patients with ALL and lymphoblastic lymphoma, or LBL.

Today, I will be discussing a unique and clinically underrepresented subgroup of patients within ALL and LBL and the challenges associated with treating the AYA population. I will also discuss some of the protocols I use in my own practice to help AYA patients with ALL achieve better long-term outcomes.

ALL is a hematologic disease that primarily affects the pediatric population. Despite this, adult patients with ALL account for 80% of ALL-related deaths, and AYA patients account for <25% of total ALL cases.[2,3]

While we do see marked improvement in pediatric ALL survival with 5-year overall survival rates being as high as 89%, for the AYA population, 5-year overall survival rates remain suboptimal, estimated to be 61%.[4,5] We remain optimistic, as we have seen more improvements in AYA patients’ overall survival, from 68% in the comparator arm of ECOG, or Eastern Cooperative Oncology Group, 1910 to 85% in the blinatumomab and chemotherapy arm of this study.[6] Improving patient outcomes and tipping the needle towards long-term overall survival and cure are the current treatment goals for AYA patients with ALL and LBL.[4-6]

Treatments for ALL or LBL involve multiagent therapies and can vary depending on genetic risks and age group. Improvement in supportive care and advances in understanding molecular genetics of the disease and utilizing minimal residual disease, or MRD, response to better stratify patient-risk have largely contributed to the overall survival of ALL/LBL patients.[3] A key reason for the steady improvements in pediatric survival rates is the incorporation of intensive asparaginase dosing into the pediatric protocol for ALL/LBL treatment.[7]

There are several key challenges unique to the AYA population, including genetic risks that are associated with their age group, complicated and non-standardized protocols, and factors related to treatment-emergent adverse events and patient tolerability.[3,6,8]

Patients in the AYA group are seen by either pediatric or adult oncologists, depending on referral patterns, which determine whether the patient undergoes a pediatric or an adult regimen. Patient care in a pediatric and adult institutions also may differ, as the treating physicians may be more familiar with one protocol over another. This makes it difficult to standardize treatment options for AYA patients with ALL.[3,8]

There is also a perceived notion of increased severity in toxicity associated with asparaginase therapy when it comes to treating AYA patients compared with pediatric patients. However, several studies have shown that AYA patients benefit more from asparaginase-intensive, pediatric protocols than previously thought.[6]

Now, we will look at currently available evidence regarding the benefits of using asparaginase therapy in AYA patients with ALL and LBL. Cancer and Leukemia Group B, or CALGB, 10403 was a large prospective clinical trial sponsored by 3 US-based cooperative groups that investigated AYA patient safety and survival outcomes when treated with asparaginase-intensive, pediatric-inspired regimen. The study enrolled 318 newly diagnosed, treatment-naïve ALL/LBL patients aged 17 to 39 years who had an ECOG score between 0 and 2 points and were confirmed to be Philadelphia chromosome-negative.[9]

Eligible patients underwent a modified pediatric protocol that consisted of 5 stages: induction, consolidation, interim maintenance, delayed intensification, and long-term maintenance therapy, which involved extensive use of asparaginase, vincristine, glucocorticoids, and CNS prophylaxis.[9]

These patients were followed up for a median of 64 months to examine their event-free survival, disease-free survival, and overall survival as a group, which were the study's primary end points.[9]

AYA patients treated with adult regimen in prior CALGB trials had a 3-year overall survival of 58%, which paled in comparison to 73% 3-year overall survival of AYA patients treated with asparaginase-intensive pediatric-inspired regimens in the CALGB 10403 study.[9]

Compared with prior CALGB studies, in which AYA patients were treated with adult regimens, AYA patients treated with pediatric-inspired asparaginase-containing regimen in this study experienced more than double the duration of event-free survival with a median of about 6.5 years and disease-free survival with a median of almost 7 years.[9] 59% and 44% of AYA patients treated with CALGB 10403 experienced event-free survival at the 3- and 10-year follow-up, respectively. 66% and 49.3% of AYA patients treated with CALGB 10403 also experienced disease-free survival at the 3- and 10-year follow-up, respectively.[9,10]

This study used prior CALGB studies, where AYA patients were treated with adult regimen, as historical control. AYA patients in prior CALGB studies experienced a median duration in event-free survival and disease-free survival of about 2.5 years.[9]

As for safety and tolerability, CALGB 10403 included treatment-related adverse events, including hypofibrinogenemia, elevated transaminases and bilirubin, hyperglycemia, and febrile neutropenia. In this study, there were 8 treatment-related deaths, accounting for 3% of the patient population, which is similar to mortality rates reported in other pediatric trials of ALL.[9]

CALGB 10403 demonstrated that AYA patients experienced significant improvements in survival outcomes when treated with pediatric-inspired regimens, which include more intense dosing of asparaginase as part of their multiagent therapies.[6] With the advent of the 10-year follow-up data, CALGB 10403 has also demonstrated the feasibility and efficacy of pediatric-inspired regimen in improving survival outcomes of AYA patients.[10]

Let's review the findings of a different study, which provides further context to the benefits asparaginase-containing therapy may offer to AYA patients with ALL.[7]

ECOG 1910 specifically focused on the outcomes of post-remission patients with Ph- ALL between the ages of 30 and 70 years. Of note, post-remission patients are patients who have previously achieved MRD-negative status. Although these patients typically have better prognosis than MRD-positive patients, they are still prone to experience relapse.[7]

In this study, patients were treated with a modified, asparaginase-containing, pediatric-inspired regimen. Their treatment schedule included 2 induction cycles followed by an intensification phase, all of which included the use of asparaginase for patients aged <55 years. Patients aged ≥55 years received a modified asparaginase dosing schedule, with its omission in the 2 induction cycles and asparaginase dose reduction in the intensification and consolidation phases.[7]

Upon achieving remission, MRD-negative patients were randomized for consolidation therapy that either included asparaginase, a chemotherapy regimen, and blinatumomab, or included only asparaginase and a chemotherapy regimen.[7]

The blinatumomab group received 4 cycles of blinatumomab and 4 cycles of asparaginase-based chemotherapy, while the control group received only 4 cycles of asparaginase-based chemotherapy.[7]

Overall, 81% of patients achieved complete remission after 2 induction cycles. MRD status was assessed after the intensification phase.[7]

Patients who achieved complete remission after induction cycles had their MRD status evaluated, which resulted in a total of 224 MRD-negative patients.[7]

These MRD-negative patients were randomized at a 1:1 ratio for consolidation therapy in the asparaginase, blinatumomab, and

chemotherapy group or the asparaginase and chemotherapy group.[7]

The combination of asparaginase, blinatumomab, and chemotherapy resulted in a superior outcome, demonstrating a 3-year overall survival of 85% compared with 68% in patients treated with asparaginase and chemotherapy, with a *P* value of 0.002. In an age-stratified subgroup analysis that compared survival outcomes in patients treated with either the asparaginase-based chemotherapy and blinatumomab or solely the asparaginase-based chemotherapy, patients younger than 55 years old saw greater benefit than patients 55 years and older. Overall, the results of this study showed the pivotal role asparaginase plays in a patient's survival during the post-remission phase when it is incorporated into the treatment backbone. It also highlights the importance of blinatumomab as a complementary therapy to be administered alongside asparaginase therapy.[7]

Using blinatumomab to complement asparaginase therapy is not exclusive to the ECOG 1910 protocol. According to a retrospective analysis of adults aged 40-60 years with Ph- ALL, it was found that about two-thirds of MRD-positive patients were treated with the CALGB 10403 backbone and complementary use of blinatumomab.[11]

In my practice, I incorporate blinatumomab between asparaginase-intensive cycles that align with the CALGB 10403 protocol instead of ECOG 1910. I have found that my patients tend to fare better this way because they have better physical and marrow recovery between the chemotherapy cycles, which positions them better for the next one.

While asparaginase-intensive therapies may be associated with toxicities such as chemical hepatotoxicity and hypersensitivity reactions, it's important to also weigh in the survival outcomes of patients who miss asparaginase doses compared with patients who complete their asparaginase regimens.[12]

In a study that looked at the impact of switching asparaginase sources and asparaginase therapy discontinuation on survival outcomes of pediatric and AYA patients with ALL, it was found that nearly all participants who opted to discontinue asparaginase therapy did so due to allergic reactions. While some participants chose to switch the source or type of asparaginase, from PEG-asparaginase to *Erwinia*-derived asparaginase, others did not.[12]

Researchers found that patients who switched from one type of asparaginase to another due to hypersensitivity reactions fared similarly as patients who had all of their scheduled PEG-asparaginase doses. On the other hand, patients who discontinued PEG-asparaginase therapy entirely without switching to a different type of asparaginase had inferior disease-free survival rates.[12]

In my clinical practice, I advocate for the use of asparaginase-based pediatric-inspired regimens for my AYA patients with Ph- ALL to optimize survival outcomes and the chance of remission and to prevent relapses, as treatment options after relapses are limited. Data from various studies, some of which we've discussed earlier in this program, showed that AYA patients experience overall improved survival outcomes when they're treated with asparaginase-based pediatric-inspired regimens than when they are treated with adult protocols.

As we've discussed, some patients, particularly adult patients, may experience toxicities associated with asparaginase therapy, which is often a reason why some oncologists are hesitant to treat their AYA patients with asparaginase therapy. So, I'm going to share a few of the best practices and treatment strategies that I use in my practice for adult patients with ALL to maximize asparaginase-based therapy and to avoid or manage asparaginase-associated toxicity.

Hepatotoxicity, which often manifests as elevated bilirubin or transaminase levels, is often transient, reversible, unrelated to liver disease, and without long-term complications. Clinical manifestations typically occur during the induction cycle and declines. In some cases, they are not observable in subsequent asparaginase-containing cycles. Some patients may see their bilirubin levels will increase after introduction to asparaginase and peak 2 weeks post-treatment, before gradually declining spontaneously.[12] Obesity and increased age are risk factors for asparaginase-induced high-grade hepatotoxicity.

However, for some patients who experience high-grade hyperbilirubinemia or grade 3/4 transaminitis, I will stop administering drugs with known hepatotoxicity. Then, I will adjust scheduling of other agents in the patient's chemotherapy treatment cycle until hyperbilirubinemia returns to grade 1 and transaminitis is at grade 2 or better.[12] But I don't stop their asparaginase treatment because there is robust data on poorer clinical outcomes for patients who miss or do not receive all their asparaginase treatment as we've discussed earlier.[12] Furthermore, to reduce the risk of severe hepatotoxicity, I reduced pegasparaginase dose to 1000 IU/m^2 and/or cap the dose to one vial for obese patients and patients 40 years or older.[13]

I've also seen cases of hypersensitivity to asparaginase in AYA patients in my clinic.

It is worth noting that asparaginase drug monitoring was not performed in ECOG 1910. As asparaginase is a bacterial-derived product

that could induce an immune-mediated response, including antibody production that could neutralize asparaginase activity, also known as silent inactivation in the absence of clinical manifestations of allergic reaction, it is possible to see asparaginase treatment failure. In this case, I would switch my patient from an *E coli*-derived asparaginase to *Erwinia*-derived asparaginase, which has limited cross-reactivity with *E coli*-derived asparaginase and is short-acting. To uncover cases of silent hypersensitivity with the routine use of premedications, I check asparaginase activity following each long-acting dose.[12,13]

Among toxicities often attributed to asparaginase is thrombosis. While asparaginase is known to reduce levels of anticoagulants, thus predisposing patients to thrombosis, the physiology of active leukemia and excessive steroid use can also induce the patient into a hypercoagulable state.[13]

In my practice, in cases where patients develop thrombosis, I manage their condition with immediate treatment with anticoagulants for at least 3 months while the patient remains on asparaginase therapy to ensure that the patient maintains adequate platelet counts. In some cases, I may also opt for platelet transfusion to improve delivery of anticoagulating agents. Asparaginase therapy can be resumed safely after a non-life-threatening thrombosis event if the patient maintained on anticoagulation with low risks of recurrent thrombosis. I avoid replacing hypofibrinogenemia with cryoprecipitate during asparaginase therapy if there is no active bleeding, as this has shown to be a risk factor for developing thrombosis.[13]

All in all, while I have seen these toxicities among others, like hypertriglyceridemia and hyperglycemia, I generally don't see them as an indication to discontinue or to reduce the dosing of my patients' asparaginase treatment. Although hypertriglyceridemia during asparaginase therapy does not require medical intervention, as it typically resolves spontaneously and rapidly, it is a risk factor for pancreatitis. Some providers may wish to treat hypertriglyceridemia, if present, to avoid pancreatitis. Pancreatitis can be observed after asparaginase therapy. Asparaginase is contraindicated in patients who develop clinical pancreatitis.[13]

So managing toxicities is key to delivering safe and effective treatment.[13]

Overall, the data we discussed today underscore the importance of using pediatric-inspired regimen in AYA patients and the benefits of asparaginase therapy in these patients. Additionally, like me, some treaters also elect to incorporate immunotherapies such as blinatumomab between intensive chemotherapy cycles as it may help patients recover between cycles and start subsequent cycles in better shape. These additional considerations are crucial when deciding on a treatment regimen. Adopting strategies like prophylactic use of corticosteroid and antihistamines as well as prompt administration of anticoagulants while monitoring my patients' platelet counts throughout, and involving my patients in these discussions, can improve my ability to effectively treat ALL and manage adverse events that occur during treatment.

We have now come to the end of the program, and I want to thank you for listening to this episode. I hope you found both the data we've discussed and some of my own practical tips useful. Thank you!

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This program was sponsored by Jazz Pharmaceuticals. If you missed any part of this discussion or to find others in this series, visit Project Oncology on ReachMD.com, where you can Be Part of the Knowledge.

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