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Patients First: Navigating Asparaginase-Based Treatment in Young Adults With ALL

Announcer:
Welcome to CME on ReachMD. This activity titled, “Patients First: Navigating Asparaginase-Based Treatments in Young Adults with Acute Lymphoblastic Leukemia,” is provided by Medical Education Resources and CMEology. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Rob Benedict:
Hi, I'm Rob Benedict, welcome and thanks for being here today. In this program, leading experts will walk you through case examples, new treatment approaches, and real-world strategies for treating ALL in young adults. Just as important, you'll hear real people talk about their experiences with ALL. Let's meet them now.

Jess:
Hi, I'm Jess, I am 36 years old. I live in Massachusetts, in Cape Cod, and I am married with a almost 4-year-old and a French Bulldog. I was diagnosed in 2014 with ALL, and I'm in marketing. I like going to the beach, hanging out with friends, music, concerts, being a mom. That’s not good.

Mike:
I’m Mike, I'm a managing director at an ad agency. I have a lovely wife and a 4-year-old daughter and another baby on the way, and our life is pretty great. Things we enjoy are cooking, outdoor, going to the beach, taking a walk, running after our 4-year-old.

Kent:
My name is Kent, I'm 33-years-old. I live in Seattle, Washington. I work for Amazon currently, I've worked there since prior to my diagnosis, and I currently am in my third year of treatment for B-cell ALL. So, I have a dog, I live with my partner. Since I have recovered from active treatment, I'm getting back into traveling, and I'm really pretty passionate about live music, so I like going to concerts. I've gotten very active in fundraising for ALL research, specifically for Fred Hutch, where I’ve received treatment.

Abbie Cobb:
Hi, my name is Abbie Cobb. Thank you, Jessica, Mike, and Kent for sharing your perspectives with us today. Now let's meet our faculty.

Dr. Cassaday:
Hi. I'm Dr. Ryan Cassaday, Professor at the University of Washington School of Medicine and Fred Hutchinson Cancer Center in Seattle, Washington.

Dr. DeAngelo:
And I'm Dr. Daniel DeAngelo from the Dana Farber Cancer Institute. I'm Chief of the Division of Leukemia and Professor of Medicine at Harvard Medical School.

Okay, let's go to our first case. Our first case involves a 24-year-old woman with a 2-week history of fatigue, dizziness, and bleeding after a dental procedure. Her white blood count is 85,000, her hemoglobin is 10, her platelet count is 17,000. The white blood cell differential shows 92% blasts, and you can see in the photo micrograph, a picture of the blast of this particular patient, and a bone

marrow was done showing greater than 90% lymphoblasts. The flow cytometry showed that the immunophenotype was positive for CD10, CD19, HLA-DR, and TdT, confirming the precursor B-cell or common ALL. It was negative for CD20, immunoglobulin, and myeloid antigens.

Cytogenetics showed a 46,XX with a derivative of chromosome 19, that is a translocation of having chromosome 1 and 19, consistent with the TCF3-PBX1 fusion. Molecular studies show that there was no Philadelphia chromosome, that is, the PCR was negative for BCR-ABL1, both the p210 and the p190 transcript, a next-generation sequencing panel was also negative. A sample was sent for probes to measure MRD after induction, that is to get an identification, so a clone that you can follow, a gene fusion, or Archer assay, confirm the translocation of TCF3-PBX1.

The patient lives with her partner and has a daughter, age 3. She works part time in a coffee shop, and lives an hour and a half away from the nearest leukemia specialty center. Enrollment in a clinical trial was discussed. She and her partner are concerned about side effects, travel to and from the specialty center. She wants to receive her care closer to her home in a community-based center. How would you proceed with her next therapy?

The definition of AYA, or adolescents and young adults, varies. Most define it as under 39, but there's some leeway to including older patients. The biggest success of chemotherapy and cancer is in pediatric ALL. And you can see the curves here where 92% or more children ages 3-9 can be cured with chemotherapy regimens from ALL. But as patients get older, the survival worsens.

Acute lymphoblastic leukemia can be subdivided in adults into both B-cell or T-cell. T-cell is less common, affecting only 20-25% of patients with acute lymphoblastic leukemia. And T-cell is further divided into classical T-cell, the more common phenotype, or something called early T-cell phenotype, or ETP-ALL. Back to the B-cell, the B-cell represents about 75-80% of cases of acute lymphoblastic leukemia, and this could be subdivided into three major categories: Philadelphia positive, Philadelphia-like, or Philadelphia negative.

There's another category called mixed phenotypic acute leukemia, or MPAL, which is very rare, and it consists of features of both acute lymphoblastic leukemia and acute myeloid leukemia.

Dr. Cassaday:
So, when we think about acute lymphoblastic leukemia in adults, perhaps the most important initial distinction is whether or not the Leukemia has the Philadelphia chromosome, or Ph positive versus Ph negative.

Starting with the Ph negative subgroup, there's generally three different categories of treatment that we usually think about, and this is typically based on the patient's age, recognizing that age is often just a surrogate for things like fitness and the presence of medical comorbidities. Young adults, including adolescents or AYA, is classically defined as those between the ages of about 18-39, and these are patients that are often offered so-called pediatric-inspired chemotherapy regimens. For middle-aged adults, or those that are a bit older, so age 40-60, these are generally patients that will get adult-inspired regimens that are a bit different in terms of intensity and content from the pediatric-inspired regimens. Lastly, for older adults, classically defined as those over age 60, because we're starting to get into an age category where the intensity of treatment becomes more of a prohibitive issue, these are often patients that need to be treated with lower-intensity regimens. Going back to the Philadelphia chromosome positive subset, many of these same principles can be applied in terms of the chemotherapy or other treatments that are administered, but the critical part here is to make sure that the treatment includes an Abl tyrosine kinase inhibitor or TKI.

The treatment of ALL is typically very complicated and often requires specialized care that sometimes is only available at specific centers, and if a patient lives a far distance from those centers, it can introduce a number of additional complexities. Because of the commitment that is required from patients going through this treatment and the toxicity that sometimes occurs, it often requires patients to rely on family members to help get them through treatment. So if the patient themselves was a caregiver or was the main source of income for a household, that could have a lot of significant impact on the members of their family and their loved ones. And then add to that the additional logistical complexity of potentially having to relocate, whether that's temporarily or on a more permanent basis, for months or longer, to undergo treatment, that can add additional complexity with respect to travel, lodging, and being displaced from your social circle and your loved ones.

So there are a lot of complexities that have to be considered when trying to figure out what treatment option is best for adults with ALL, and this can be particularly important for adolescents and young adults, because those preferred pediatric-inspired therapies that we generally recommend are very difficult to administer in community practices that aren't as familiar with them because of their complexity, their intensity, and the inclusion of drugs and procedures that are not as familiar to a community oncologist.

So, when deciding on a treatment for any particular patient with ALL, certainly the biological characteristics, the patient's medical comorbidities are really, really important. But you also have to pay particular attention to the social situation that the patient is in to

understand what treatment is going to be feasible, particularly if it's a situation where, again, someone is needing to relocate a long distance, or maybe seeking an opportunity where they can have their care co-managed by a specialty center and potentially one closer to their home.

Rob Benedict:
Adolescent and young adults with ALL have unique medical and psychosocial needs. A comprehensive approach is needed to meet the needs of patients in this age group.

Dr. DeAngelo:
There's many considerations when treating the AYA patient population for acute lymphoblastic leukemia. Ryan's already gone over the differences in the leukemia biology and treatment approaches, but focusing on the right hand of the slide, there's many psychosocial factors. Remember, these are patients that are just emerging as adults. Some have children, some want to have children. Financial stressors, a new parent who gets diagnosed with ALL is going to have a lot of financial issues, especially if they're the primary financial responsibility in the household. Issues with fertility or sexuality, social determinants of health, all of these issues factor into considerations for the treatment. And these can often be addressed by survivorship clinics that many of the referral centers will have.

Kent:
Before I found out I had ALL, I was at the peak of my life. I had just turned 30, my career was really taking off at Amazon. I was on track for my next promotion, my life was full. I was traveling, you know, internationally, lot of friends, lot of adventures. Everything seemed to be moving in the right direction, and then everything came to a grinding halt with the diagnosis.

Jess:
My finances were impacted after diagnosis pretty significantly. I had to stop working. I did get to take a leave of absence, and my job was protected, to a degree. When I got back almost a year later, I had been demoted to a different level.

Abbie Cobb:
Jessica and Kent talked about how an ALL diagnosis affected their lives, but ALL can also affect other people and relationships. Let's hear Jessica's husband, Mike, describe how ALL affected him.

Mike:
I remember the first week very clearly. I mean I dropped everything at work, I told my work I wasn't coming in. Immediately I was very focused on just trying to be there, be supportive, do everything I can. My entire life was impacted after I found out she had ALL. I mean, you're not able to—I wasn't looking to hang out with my friends. All of my friends were in contact, wondering what's happening, but we were very conscious of, one, not getting ever sick, because she was neutropenic for so long at the beginning, and that just makes you almost manic. You feel very isolated.

Dr. DeAngelo:
There have been several advances in the treatment of patients, specifically AYA patients with ALL. Better definitions of the cytogenetic and molecular subtypes use of asparaginase-based or pediatric-inspired regimens. Importantly, the ability to detect minute evidence of disease, referred to as measurable residual disease, or MRD, and new therapeutic approaches, including tyrosine kinase inhibitors and immunotherapy.

Pediatric-inspired regimens differ from traditional adult protocols. They contain high doses of asparaginase, including cumulative doses of asparaginase, vincristine and glucocorticoids, as compared to the traditional adult regimens. They do include intensive or prolonged central nervous system, or CNS, prophylaxis. And allogeneic transplant is only used for very high-risk patients. Traditional adult protocols typically avoid asparaginase, they use more myelotoxic or myelosuppressive agents such as anthracyclines or cyclophosphamide. Examples are hyper-CVAD, but there's other examples. And more frequent utilization of allogeneic transplant.

The outcomes for adolescent and young adults, or AYA, have improved over time compared with those of other regimens. Listed here are some of the pediatric inspired regimens, the CALGB 10403 that Dr. Wendy Stock used, which is an international cooperative group trial which treated patients 17-39 with an event-free survival of almost 60% and overall survival at 73%. This really revolutionized the care. At the Dana Farber, we have adapted pediatric regimens used for patients 1-18 into the older AYA population 18-50, have been able to also show improvement of outcome. The German group, from the Jamal group, or the French Grail group, or the northern Scandinavian NOFO group, have also employed pediatric-inspired regimens, and you can see from the table, have improved on the event-free and overall survival that we showed previously.

ASH guideline recommendations for the treatment of patients with ALL in the AYA patient population. ASH has initiated a guidelines approach to try and guide physicians who may not be experts in the treatment of AYA. And the question that was asked is, what's the

best frontline treatment approach for adolescents and young adults with B-cell or T-cell acute lymphoblastic leukemia, receiving frontline therapy? That is, what are the comparative benefits or harms of asparaginase-containing regimens such as CALGB 10403, compared to those with non-asparaginase-containing regimens like hyper-CVAD. And the recommendations from the ASH guideline committee is that for patients who in the AYA patient population 18-39 with either B- or T-cell acute lymphoblastic leukemia or lymphoma, receiving frontline therapy, that the ASH guideline panel recommends that pediatric-inspired regimens, that is those containing asparaginase regimens, are strongly recommended based on moderate certainty of evidence.

Measurable residual disease, or MRD, is a very important augmentation to the management of treatment for patients with ALL. It allows us to measure minute, leftover quantities of disease. There's lots of different approaches, multicolor flow cytometry, or MFC, which has the lowest sensitivity. But the advantage of showing

an amino phenotype, which can guide therapy. The sensitivity in most assays is around 0.01 or 1/10,000. RT-PCR and next generation high-throughput sequencing with the others. The only FDA approved is the NGS, or high-throughput sequencing, which has a remarkable sensitivity about 1 cell in a million. This allows us to again measure persistence, low level disease and can guide subsequent therapy.

It's important that the type and the assay or the sample is appropriate. That is, it should be the first pull of the bone marrow, and it should be a cellular pull. You need at least a million events in order to be adequate and accurate. And the timing and testings vary depending on the regimen. It's important to interact with the leukemia subtype and genomic alterations as this can vary between the identification; for example, B-cell or T-cell, or if a patient has a KMT2A-rearranged leukemia. The role of more sensitive tests and how to use these new approaches is less clear.

Frontline immunotherapy for patients with acute lymphoblastic leukemia is very important. Blinatumomab, for example, is a CD3/CD19 bispecific T-cell engager. What it does is it directs the patient's own T-cells to kill the CD19-positive lymphoblasts. The improved indication is for patients greater than 1 month with CD19-positive B-cell ALL in first or second remission, which are with MRD-positive disease, anybody with relapsed or refractory CD19-positive leukemia, or patients with CD19-positive, Philadelphia-negative B-cell ALL in consolidation, that means that those patients are MRD negative. So, these are three important FDA approved indications.

The NCCN also recommends and guides, very similarly to the package approval that is combined with TKI CD19-positive, Philadelphia-positive B-cell ALL for use in consolidation after chemotherapy, and in the relapsed/refractory setting. Administration is by a continuous IV infusion for 28 days with 2 weeks rest. Typical toxicity includes cytokine release syndrome as well as neurotoxicity, including immune effector cell-associated by neurotoxicity, or ICANS.

Rob Benedict:
Asparaginase is a critical part of treatment for children, adolescents, and young adults with ALL, but many clinicians have limited experience using it. What do clinicians need to know about using asparaginase?

Dr. DeAngelo:
Asparaginase has a unique mechanism of action. Leukemic lymphoblasts cannot make asparagine. Therefore, they need to import asparagine from the plasma in order to survive. In the plasma, asparaginase converts asparagine to aspartic acid and ammonia, therefore depriving the cancer cell, in this case, the lymphoblast, of an important asparagine, and therefore the cells are destroyed.

It is important to administer asparaginase per the protocol, and that what was discovered, retrospectively, is that missing doses, or skipped doses, due to toxicity or compliance is associated with inferior outcomes. Asparaginase is a very critical and key component of the pediatric-inspired regimens for patients, AYA patients in particular, with acute lymphoblastic leukemia. Favorable outcomes are associated with sufficient and prolonged serum asparagine depletion. And retrospective analysis shows a negative impact on early discontinuation, usually due to toxicity concerns.

There are several asparaginase formulations that are approved for use in the United States. Pegaspargase, which is an E. coli pegylated form, is first line indication for both children and adults. Calaspargase is also a pegylated form from E. coli, and its use is limited to patients 1 month to 21 years of age. A third product is from Erwinia chrysanthemi, and this is a non-pegylated asparaginase. It's a recombinant asparaginase, and it is approved for patients greater than 1 month, who have developed hypersensitivity to an E. coli-derived asparaginase compound.

And now I'll turn it over to Ryan.

Dr. Cassaday:
Earlier this year, a consensus statement generated by 12 ALL experts was published in the journal *Haematologica*. The approach to asparaginase therapy in ALL should involve multiple different steps. First, as Dr. DeAngelo mentioned earlier, it's important to aim to

give the full intended course of asparaginase to avoid missed doses when possible. Toxicity should be mitigated where feasible, and risk for toxicity should also be considered preemptively, including older age, higher BMI or obesity as well as medical comorbidities. Asparaginase activity levels can be monitored. When adverse events develop, these should be managed, and then where appropriate, asparaginase therapy should be modified.

Dr. DeAngelo:
There's an impact of obesity on outcomes with asparaginase-containing regimens in AYA patient populations. These have been observed from several groups. The NCTN group, both Dr. Stock and Dr. Advani published independent papers looking at the impact of obesity that was associated with a decrease in the disease-free survival, as well as was associated with an increase in high-grade, that is grade 3 or 4 toxicities.

Our group here at the Dana Farber looked at a pediatric and adult group ages 15-50, and showed that patients who were obese or overweight not only had more hepatotoxicity and hyperglycemia, but actually had a significantly worse overall survival and event-free survival, overall survival leading to from relapse. And this is despite several rates of toxicity in younger patients.

Dr. Cassaday:
Because of asparaginase's unique mechanism of action, it has a variety of class-specific toxicities that should be understood, but it's important to recognize that these are generally manageable, reversible, and importantly, non-fatal. Immune-mediated toxicities are generally hypersensitivity reactions, which can include both a clinical hypersensitivity reaction that is readily apparent, but also a silent inactivation, where neutralizing antibodies are produced but there are no clinical manifestations of it, so no symptoms of a reaction.

The nonimmune-mediated reactions are quite varied. There are instances of thrombosis, including unusual manifestations of thrombosis, such as cerebral vein thromboses, you can also see increased risk of hemorrhage. Hepatotoxicity, including elevated transaminases and elevated bilirubin. Pancreatitis is one of the most feared complications of asparaginase. There are increased rates of osteonecrosis. Hypertriglyceridemia is often observed, as well as hyperglycemia. And hyperammonemia can also occur because of the biochemical effect of producing ammonia by converting asparagine to aspartic acid.

Kent:
When my doctor explained asparaginase as part of my treatment plan, he told me he was very upfront on the fact that it is arguably the most important drug of your protocol. It's very critical for targeting leukemia cells, but it is also very tough on the body, especially the liver. So, he was very upfront and honest with me about everything, and I think that helped me kind of know what I was in for.

Dr. Cassaday:
A critical distinction with respect to allergic reactions that can occur during treatment with asparaginase is whether or not these represent a clinical hypersensitivity reaction or an infusion-related reaction. From a pathophysiology perspective, the hypersensitivity reactions are thought to be antibody mediated, whereas the infusion-related reactions are not antibody mediated. You can see an overlap in terms of the clinical manifestations of this that can make it difficult to distinguish between these two reactions, so things like hypotension, shortness of breath, fever, anxiety, all of these can be observed regardless of the underlying mechanism. But there are some clues with some symptoms being a bit more specific for one group of side effects or the other. So, for example, the hypersensitivity reactions, you're more likely to see things like wheezing, stridor, angioedema, whereas the infusion-related reactions, you're more likely to see elevated blood pressure, facial flushing, rigors or chills, and muscle cramping.

There are additional clues that can help distinguish between a clinical hypersensitivity reaction or an infusion-related reaction beyond the specific symptoms that were discussed on the previous slide. So, as I mentioned, a clinical hypersensitivity reaction is generally thought to be an antibody-mediated reaction, whereas an infusion-related reaction is non-antibody mediated and thought to be anaphylactoid or potentially related to the increase in ammonia that can be seen from the biochemical reaction that asparaginase causes.

Another clue can be the timing in the treatment course. So, because you need antibody formation in order to have the hypersensitivity reaction, it generally does not occur until the second or third dose of an E. coli-derived asparaginase. So, it's very rare to see this during the initial treatment cycle. But on the other hand, an infusion-related reaction often will happen with the first dose when the patient is first exposed to the drug.

A hypersensitivity reaction will often start within minutes of starting the IV infusion, again, because it is being caused by preformed antibodies from the exposure that occurred previously. But it sometimes can be delayed, particularly in cases if the medication is being delivered intramuscularly, which is generally not very common anymore, but if it is given intramuscularly, the reaction can be delayed just because of the different pharmacokinetics. On the other hand, for an infusion-related reaction, this can happen during or even shortly after the infusion because of the timing of onset.

Another key distinguishing feature, if being employed, which is strongly recommended for the use of asparaginase, is the result seen from therapeutic drug monitoring, specifically the trough serum asparaginase activity level. So again, because the hypersensitivity reactions are thought to generate neutralizing antibodies, these will generally cause rapid clearance of the asparaginase and thus very low or undetectable levels of asparaginase activity several days later. On the other hand, for an infusion-related reaction that increased clearance of the medication is generally not observed, so as long as the patient was able to receive most or all of their intended dose, there should still be adequate levels of asparaginase detected.

There are two types of hypersensitivity reactions to be aware of, and both are thought to be mediated by antibodies directed against the asparaginase molecule. The one we generally think of would be a symptomatic clinical hypersensitivity reaction with classical allergic reaction type symptoms, approximately 3 to as much as 24% of patients given pegaspargase will have these reactions. The severity can range from things like mild symptoms, like urticaria, all the way up to a systemic reaction that can be life threatening, such as anaphylaxis. And when this happens, it's important to note that this is almost always associated with inactivation of the asparaginase dose that was just administered, even if the reaction is mild.

However, there is also a phenomenon of silent inactivation, where the same underlying pathophysiology of an antibody-mediated destruction of the drug is happening, but in the absence of clinical symptoms. These are relatively rare, probably less than 10% of patients given pegaspargase will experience this. And the only clue present may be the lack of significant asparaginase activity levels when measured several days after the dose. And there are some pre-defined thresholds that are thought to be most suggestive of this, particularly when that asparagine is activity level is less than 0.1 IU/mL, measured about 7 days later, or if it's undetectable, less than the lower limit of detection, 14 days after the dose is given.

And it's important to know that patients that have a clinical hypersensitivity reaction or the silent inactivation can have inferior outcomes unless their pegaspargase is replaced with an Erwinia-derived asparaginase that is able to get around the underlying immune inactivation.

ASH guidelines have also provided recommendations about how to address hypersensitivity reactions to asparaginase. So, the question posed to this body was that adolescents and young adults with ALL receiving frontline asparaginase who have an asparaginase-related reaction or an allergic type reaction, what are the comparative effects and toxicities of desensitization versus the use of an alternative asparaginase product, specifically recombinant Erwinia-derived asparaginase. And ultimately, the recommendation is that in this setting, for frontline treatment of it with a pediatric-inspired regimen, it is generally recommended that patients switch to an Erwinia-based product as opposed to undergoing discontinuation, and that's

based on a strong recommendation, but with a low certainty of evidence. The panel, however, was unable to provide a recommendation related to desensitization, because the evidence in this setting is relatively thin, particularly in a setting where there are alternative asparaginase products available. The panel ultimately concluded that the benefits, such as improved survival and disease control, outweigh the drawbacks, including the high cost and resources required for the Erwinia-based treatment.

Switching or substituting the Erwinia-derived asparaginase in place of E. coli-derived asparaginase has some nuance to it as well. So, the timing of when to switch is important. So again, if there's a clinical hypersensitivity reaction to an E. coli-derived product, such as pegaspargase or calaspargase pegol. Generally, if the reaction is mild, such as grade 1 or grade 2, it may be prudent to wait and see the follow-up serum asparaginase activity level to confirm the suspicion before making any changes to the treatment. On the other hand, if it's a more significant or grade 3 or higher reaction, very suspicious for an antibody-mediated reaction, it is often prudent to immediately switch to an Erwinia-based product without checking the asparaginase activity level. The idea there is waiting for that level to come back when you already have a very high pretest probability is ultimately just going to mean more time that the patient goes without asparagine depletion.

On the other hand, a silent inactivation type of reaction, you're not going to have those clinical symptoms to guide that decision. Here, you're largely, if not exclusively, relying on that follow-up asparaginase activity level, which again, if it's less than 0.1 at day 7 from the dose, or below the lower limit of detection at day 14, that is when you have to suspect cell and inactivation. And at either of these times, that is when it's most important to switch products.

However, if it's an infusion-related reaction, following some of those features we described before, it is generally not necessary to switch. You can continue to give the E. coli-derived product in that situation, but again, perhaps with different premedications or different methods of administration. Ultimately, the goal here is to try to maintain consistent asparagine depletion and thus therapeutic efficacy with the drug. Holding and restarting the drug will not achieve this, which is why it's important to substitute quickly if suspected, promptly when identified, because switching to an Erwinia-derived asparaginase product ultimately will help avoid compromising disease-free survival. Recombinant Erwinia-derived asparaginase, importantly, does not have immunologic cross reactivity with E. coli-

derived asparaginases, which is why it can be substituted in cases of hypersensitivity to E. coli-derived products.

The first study that really helped demonstrate this was the Children's Oncology Group AALL1931 study, this included 228 patients at a median age of 10, but again notable, the age range went up to age 25, so some young adults were included in this trial, and all patients developed a hypersensitivity reaction or silent inactivation to the E. coli-derived asparaginase product they were administered. These patients were then switched to this recombinant Erwinia-derived asparaginase product. And because of the shorter half-life of this product, they had to receive six doses in order to replace one dose of a long acting E. coli-derived asparaginase.

Importantly, the safety profile of the Erwinia product was consistent with E. coli-derived asparaginase. They have essentially the same mechanism of action, so the toxicity profile, fortunately, was pretty similar.

And this ultimately led to US FDA approval of recombinant Erwinia asparaginase in this setting. And there are different dosing strategies that can be employed. In settings where it's possible to administer doses every 48 hours. So, in other words, places that can include administering on the weekends, the dosing is typically 25 mg/m^2 intramuscularly every 48 hours. And when that is done, 96% of patients are able to achieve what are thought to be therapeutic levels of nadir asparaginase activity level.

The alternative dosing strategy, which is mostly employed in places where weekend administration is not feasible, is on a Monday, Wednesday, Friday schedule. And you can see, because of that longer time between the Friday dose and the Monday dose, the dose that is given on Fridays is higher. So, it's 25 mg/m^2 IM on Mondays and Wednesdays, and then 50 mg/m^2 on Friday, preferably in the afternoon, again, to just to every possible opportunity to shorten the dose interval from Friday to Monday. And by doing that, you still achieve more than 90% of patients reaching that asparagine activity levels thought to be therapeutic.

Premedication is another important aspect of administering asparaginase products. These typically include corticosteroids, acetaminophen, antihistamines, typically given 30-60 minutes before each dose of asparaginase. These can reduce the symptoms of hypersensitivity and infusion-related reactions, but it is important to recognize that they are not thought to prevent the development of neutralizing antibodies. So, what does that mean? This is where the issue of silent inactivation comes in, is that this can potentially mask important signs or symptoms of immune system activation if an antibody was formed against the asparaginase product.

Therefore, particularly in a setting where premedication is given, therapeutic drug monitoring is very important.

Dr. DeAngelo:
As Ryan discussed, there are pegaspargase therapeutic drug monitoring. These are easy and can be easily done at any center. Typically, pegaspargase drug monitoring occurs weekly. So, for example, if a weekly level 7 days after asparaginase administration is less than 0.1 well, the patient doesn't have therapeutic levels, and therefore one can confirm that, needs to confirm that, and if confirmed, switch to a different asparaginase preparation. Similarly, if after 2 weeks of asparagine administration, the asparaginase level remains very low, again, alternative asparaginase regimens are available, and this will help the investigator and the physician identify those patients who develop silent antibodies.

So, let's go with our third case. This is a 39-year-old woman with a mediastinal mass that was diagnosed by biopsy with the T-cell acute lymphoblastic leukemia. She has several comorbidities, including a high BMI of 34, type 2 diabetes mellitus, and hypertension. Midway through induction therapy on an asparaginase-based regimen, she develops left calf swelling, and a Doppler ultrasound shows a thrombus in the left femoral and popliteal veins. So how would you treat this patient, and should this patient have received a medication for thromboembolism prophylaxis?

So, Ryan, how would you treat this patient at your center?

Dr. Cassaday:
You know, traditionally, low molecular weight heparin is the preferred product in this situation, I think specifically asparaginase-associated thrombosis, and that's still mentioned in, you know, expert guidelines and so forth. But I'll be honest, while the data are not as strong, we have a number of patients who we'll treat with some of the newer DOAC class of anticoagulants. The theoretical advantages are because they do not work directly through antithrombin, they potentially have the benefit of getting around what is thought to be the precipitating factor of some of these thromboses, it's thought that asparagine depletion leads to transient deficiency of antithrombin, and since that's how heparin exerts its effect, drugs like apixaban and rivaroxaban and in that class of medications they, you know, they're direct anti-10 inhibitors so they kind of get around that. But admittedly, the evidence is not as strong. So, if patients take those and their thrombosis persists or worsens in some way, then we'll often switch to low molecular weight heparin.

Dr. DeAngelo:
What about your approach to prophylaxis, both in terms of anticoagulation with heparin or a DOAC as well as AT3 repletion, does your center do that?

Dr. Cassaday:
We are rather minimalistic in our approach to this problem, certainly for patients that are, you know, hospitalized that don't have significant thrombocytopenia, we'll use, you know, traditional general medical approaches to pharmacologic thromboprophylaxis, low-dose low molecular weight heparin and so forth. But beyond that, we're not usually using prescription medications for ambulatory patients, and we don't routinely monitor and replete antithrombin levels at our center.

It's important to remember that in general, thrombosis is much more common than bleeding in the setting of asparaginase-based therapy. So, for example, studies in adults have identified that thrombosis can occur anywhere from about 10-27% of cases, whereas hemorrhage is much less common, generally less than 5%.

Most thromboses that occur are lower extremity or catheter-associated VTE. It's particularly important to remember the catheter-associated ones, because again, all these patients in general are going to have central venous catheters. You can however, see pulmonary embolism, arterial thromboembolism, cavernous sinus venous thrombosis. Fortunately, these are quite rare, but of course, because of their manifestations, they can potentially be life threatening or even fatal.

And as was alluded to before, there is a very interesting mechanism behind this, which is basically thought to involve relative depletion of natural anticoagulant proteins relative to others. It's important to remember that these effects can also be exacerbated by other things that are going on, such as liver dysfunction or the use of corticosteroids, which of course, are a critical component of treating some of these patients with asparaginase-based therapy.

There are some recognized risk factors for thrombosis in the setting of asparaginase therapy: older age, obesity, patients with a lower white count or those with a mediastinal mass also are at greater risk. In terms of the current evidence, the standard treatment for venous thromboembolism is generally comprised of a low molecular weight heparin or direct oral anticoagulants, or DOACs, though, as we discussed before, there's less evidence to support these, and that it is generally advised to continue anticoagulation until all the doses of pegaspargase have been given, remembering to account for the relatively long half-life of that drug, so generally, for at least a few weeks in our practice, beyond the last dose.

In the event of active bleeding, it's important to remember the potential use of cryoprecipitate again to understand the potential association of reduced fibrinogen as that is the preferred blood product to replete that specific factor. And when questioning whether or not to rechallenge a patient who's experienced one of these events, VTE, including the cerebral sinus venous thrombosis, is not an absolute contraindication to future asparaginase dosing when considering the risks and benefits, but again, a central venous sinus thrombosis is often much greater risk than a catheter-associated upper extremity thrombosis, which is why the risk-benefit ratio really needs to be considered.

There are different prophylaxis strategies available for these complications, though, as we discussed before, the evidence that supports them is somewhat mixed. Routine prophylaxis is generally not recommended across the board, but it can certainly be considered in patients that are thought to be at increased risk, who will receive and require frequent or intense asparaginase therapy. And along those same lines, routine antithrombin replacement is also typically not recommended.

In terms of the risk of bleeding, it is generally recommended that prophylactic administration of cryoprecipitate not be performed, and it can actually increase the risk of VTE, again, because of that balance between the natural anticoagulants and procoagulants. So that is why it is generally only recommended to use cryoprecipitate in the setting of active bleeding.

Another very common and important manifestation of toxicity from asparaginase is hepatotoxicity. This is actually the most common adverse event related to asparagine is when treating adults. The mechanism behind this is thought to involve impaired mitochondrial function as a consequence of asparagine depletion, and because mitochondria are very important in metabolizing fatty acids, that leads to a relative accumulation of this in cells, particularly hepatocytes. You can see elevated bilirubin grade 3 or 4 in as many as 20-30% of patients. You can also see significant elevations in the transaminases, potentially even more than half of patients experiencing this. But it's important to remember, this is generally associated with a low risk of significant morbidity. It's transient. Overt hepatic failure from this is exceedingly rare. Risk factors include older age, higher BMI, and giving higher doses of pegaspargase.

There is admittedly relatively little evidence to support particular prevention or treatment strategies. Reducing the dose of pegaspargase, whether that's based on their weight, or capping the dose at a particular level, may reduce the risk. Changing the drug sequence of other drugs that are given to potentially avoid compounding or exacerbating the toxicity can sometimes be considered. So, for example, there have been studies that have given anthracycline a different time to avoid potentially sort of two hits against the liver at the same time. L-carnitine has been used as a treatment for hepatotoxicity and is actively being studied as a prophylactic strategy.

And it's important to remember again, because of the transient nature of this and the critical importance that asparaginase has in

treatment, you can rechallenge after these toxicities, including after severe toxicities, but it's typically a good idea to wait for the next dose of asparaginase to occur until the bilirubin and transaminases have improved so that you reduce the risk of exacerbating or causing more hepatotoxicity with the future cycles.

Dr. DeAngelo:
Pancreatitis is one of the more feared complications of asparaginase, but fortunately, it's rare. Risk factors include older age, more intensive or prolonged exposure, and, of course, genetic predisposition. It's important to differentiate chemical pancreatitis that is a asymptomatic elevation of the serum lipase and amylase from clinical pancreatitis associated with symptoms of pain as well as radiographic images of pancreatic inflammation. This can cause significant morbidity and even death. Treatment is prompt, supportive care. And in general, I do not rechallenge, nor is it recommended to rechallenge with any asparagine or an alternative asparaginase regimen. Usually when clinical pancreatitis occurs further, asparaginase is avoided.

Dr. Cassaday:
A word on asparaginase dosing, admittedly, the optimal dose and frequency of pegaspargase for adults is somewhat unclear. This is in part due to the relatively limited studies that are done in this population compared to the pediatric population. Reducing the dose of pegaspargase in adults down to ranges of 1000-2000 IU/m^2 can adequately deplete serum asparagine levels comparable to what is seen with the more traditional pediatric dose of 2500 IU/m^2. Many centers will implement dose capping of pegaspargase. In other words, a single vial of the drug typically includes 3750 IU, so giving that dose and no more can perhaps be helpful at reducing toxicity in adults, but admittedly, the evidence is exclusively retrospective and somewhat limited and conflicting.

So Dan, can you tell us a bit about how you all approach asparaginase dosing at your center?

Dr. DeAngelo:
Yeah so, we've had a long history, as you know, of using our pediatric-inspired approaches. And what we've done with the pegylated forms is cap. That is, one vial is 3750 as you mentioned previously. And as a result, as you get larger and higher BMI, the result is actually to effectively reduce the dose. We don't use individual optimal BSA consideration. So, by capping the dose, we kind of mitigate some of the toxicities associated, and we use 2000 mg/m^2, as opposed to the pediatric dosing.

Dr. Cassaday:
Yeah, we do something pretty similar, where we'll routinely cap at one vial. In fact, our treatment plans in our EHR are built to automatically institute that. In terms of situations where I might consider reducing the dose even further are probably people who, again, are thought to be at particularly high risk of asparaginase-associated toxicity. Like you said, older adults. I will sometimes also include this for patients that have a very high BMI. But beyond that, generally, I would say most adults that I treat, because of the size that they are, are largely getting a flat dose of 3750.

Abbie Cobb:
You've heard a lot today about ALL and asparaginase-based treatment for young adult patients, let's hear the top five takeaways from our experts.

Dr. DeAngelo:
So, let's review the five things to know about asparaginase-containing regimens for acute lymphoblastic leukemia.

I'll start. The first one is that asparaginase-based regimens improve outcomes, specifically for AYA patients, compared to traditional adult protocols.

Dr. Cassaday:
Next, the efficacy really depends on sufficient and sustained levels of asparaginase activity.

Dr. DeAngelo:
There are three asparaginase formulations that are available in the United States, an E. coli-derived pegaspargase is used often upfront with recombinant Erwinia-based or derived reformulation is reserved for patients who develop immune-mediated hypersensitivity to the pegylated form of asparaginase.

Dr. Cassaday:
While asparaginase can cause a range of toxicities, it's important to remember that these can usually be mitigated, monitored, and managed.

Dr. DeAngelo:
It's also important to note that measuring serum asparaginase levels can detect silent inactivation and can help distinguish between a

hypersensitivity reaction from other infusion-related reactions.

Dr. Cassaday:
So, in conclusion, when thinking about acute lymphoblastic leukemia in adolescents and young adults, some of the challenges that we've discussed include making sure to increase the use of pediatric-inspired regimens, which can help improve

outcomes, as well as discovering new, more effective and less toxic treatment strategies.

Dr. DeAngelo:
Some solutions and opportunities for further improvement include increasing access to pediatric-inspired regimens outside of the specialty centers, I think this is really important, disseminating new ASH recommendations on ALL treatment in the AYA population, the integration of emerging therapies based on new evidence, increased enrollment of adolescents and young adults in ALL clinical trials, another very important point, and then to provide comprehensive, multi-disciplinary care, to meet the unique needs of this AYA population.

Rob Benedict:
Let's hear again from Kent, Jessica, and Mike. How did having ALL change their lives? What are they looking forward to now?

Kent:
Looking forward, I see my future is extremely bright, which I'm very excited about. I have 6 months left in treatment. I think one thing that I gained from treatment is the kind of advocacy aspect. I think it made me, I mean, it really breaks you down to your core and builds you back up. So, I think I'm much more confident than I was. So, I think getting back into my career, I feel very confident in that. I'm very excited to finish treatment and go backpacking through Europe. I've already kind of started going back out and seeing live music again, getting back into restaurants, and I think I have a bright future ahead. I'm very thankful for the opportunity to go through this treatment and have the opportunity to continue living.

Jess:
I would say that my life has been, I think, better for the cancer experience. And I say that 100% genuinely. I think I'm a better person because of what I went through. I think I'm stronger. I think I have more empathy for people. I think I'm more compassionate of what other people are going through.

Mike:
So now, as we look ahead, there's so much great things that's up and coming, you know, whether that's moving on to the next home or job or having another child on the way with another adventure. And there's just a lot, you know, family trips and vacations and normal life. Living a normal, fun life just sounds amazing, and I think we value it a little bit differently at times, knowing that it got so close to being taken away.

Abbie Cobb:
Patients and caregivers want trusted sources of information about ALL, here are some websites you can share with your patients. Blood Cancer United, formerly, the Leukemia and Lymphoma Society, American Cancer Society, National Comprehensive Cancer Network, National Cancer Institute. You can also find videos, especially for patients, at our website, conversationsaboutall.org.

Rob Benedict:
Well, that wraps things up for us today. Thank you, Kent, Jessica, and Mike for sharing your experiences with us, and thanks to Dr. DeAngelo and Dr. Cassaday for explaining ways to improve outcomes for young adults with ALL. We hope you'll use what you learned in your own practice. We know how busy you are, so thank you.

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