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Minimal Residual Disease & the Future of B-Cell ALL Treatment

Announcer: This is ReachMD. Welcome to this medical industry feature, Minimal Residual Disease & the Future of B-Cell ALL Treatment," sponsored by Amgen. This program is intended for physicians.

Amgen provided funding for this podcast and compensated the presenters for participating in this program. This program is not independent medical education and is not eligible for CME credit. Here is your host, Dr. Jennifer Caudle.

Dr. Caudle: When it comes to managing acute lymphoblastic leukemia, or ALL for short, there's been growing discussion about the prognostic value of minimal residual disease, or MRD. With research showing that MRD is a strong predictor of relapse in adult patients with ALL, *and* now that we have BLINCYTO® (blinatumomab), the first and only therapy indicated for the treatment of MRD(+) B-cell precursor ALL, the value of MRD testing can no longer be ignored.

Welcome to ReachMD. I'm your host Dr. Jennifer Caudle, and joining me to shed some light on the importance of MRD testing is Dr. Daniel DeAngelo from the Dana-Farber Cancer Institute in Boston, who specializes in the management of patients with acute lymphoblastic leukemia. Dr. DeAngelo, welcome to the program.

Dr. DeAngelo: Thank you for having me, I'm excited to be here.

Dr. Caudle: Dr. DeAngelo, why don't you start by telling us how minimal residual disease is defined. How does MRD testing fit into your everyday treatment protocol?

Dr. DeAngelo: Thank you. MRD means that there are a relatively small number of leukemic cells in the blood after a patient has achieved remission. MRD is generally defined as having leukemic cells that cannot be detected by traditional techniques using a microscope for example, but can be detected by tests with sensitivities such as one leukemic cell out of 10,000 or (0.01%) or as sensitive as one leukemic cell out of 1,000,000 or (0.0001%) with tests that are available today. The presence of MRD is a strong predictor of relapse, and achieving MRD-negative status early in the course of treatment has been shown to give patients a reduced risk of relapse and a stronger chance for longer overall survival.

I strongly believe that MRD testing should be an essential aspect of how we manage patients in remission. When I'm collecting a bone marrow aspirate from a patient with ALL who is in remission, I always test for MRD using the first or early pull of the bone marrow aspirate. I am looking for a deep response after completion of initial induction treatment, and then in subsequent samples after additional treatment, I'm looking for signs of early relapse. Recent updates to the NCCN Clinical Practice Guidelines in Oncology, [or NCCN Guidelines® for short], recommend MRD testing.

Announcer: Yes, that's right. The NCCN Guidelines® recommend MRD testing at the following points during the patient journey: at baseline during diagnosis for all patients, immediately following induction therapy if a patient has achieved complete remission (including both Philadelphia-chromosome positive and Philadelphia-chromosome negative adolescent, young adult, and adult patients), if a patient relapses or is refractory to prior therapy and MRD testing is not previously done (including Philadelphia-chromosome negative adolescent, young adult, and adult patients), and during post-consolidation surveillance if a bone marrow aspirate is done (as clinically indicated every 3 to 6 months for at least 5 years).

It is also important to note that the procedure for collecting bone marrow samples can impact the test results, so to follow best practices for MRD testing when pulling bone marrow samples. For example, the sample for an MRD analysis should be the very first aspirate drawn from the bone marrow, and based on my clinical experience, should contain only two to three CCs of bone marrow aspirate. MRD can be measured by quantitative flow cytometry, polymerase chain reaction, or next-generation sequencing. In my experience, if one is

using flow cytometry, which is the most common technique used in the United States, then at least one million events should be assayed in order to have the ability to detect a small MRD population.

Dr. Caudle: And what do you think are the most important reasons to test for MRD?

Dr. DeAngelo: That's a very good question. Completely eradicating disease is the most important factor for a patient to achieve long-term survival. Achieving MRD negativity will bring my patients closer to a cure. For patients with ALL that achieve hematological remission, I think that MRD is the most important discriminator in determining the likelihood of relapse. MRD negativity is a very important prognostic factor in terms of predicting a patient's overall survival.

Even though the data are evolving, they suggest that MRD(+) patients are more likely to have a poorer outcome after a stem cell transplant. And therefore, MRD assessment is essential for all patients prior to proceeding to a stem cell transplantation.

Dr. Caudle: So, what do you do with a patient who has MRD following induction treatment? Has the availability of BLINCYTO® (also known as blinatumomab) impacted your practice?

Dr. DeAngelo: For patients who are MRD(+) after induction therapy, I usually consider changing treatments to potentially eliminate MRD and improve their prognosis with the goal of getting them to an allogeneic transplant when possible. The availability of BLINCYTO®, the first and only immunotherapy indicated for the treatment of MRD(+) B-cell precursor ALL, gives my patients a different approach. It should be noted that this indication is approved under accelerated approval as a responder analysis based on MRD response rate and hematological relapse-free survival.

For my patients who are MRD(+), but who are not candidates for stem cell transplant, I still use BLINCYTO® for up to 4 cycles with the goal of eliminating residual disease. Converting patients to MRD(–) helps improve outcomes versus patients who remain MRD(+).

For my MRD(+) patients who are CD19(+) (which accounts for most patients with B-cell precursor ALL), I will often administer blinatumomab following induction therapy to convert them to MRD(–) status when possible. Now with BLINCYTO®'s indication for MRD(+) patients, it's great knowing that, for the first time, we have a therapy that can potentially eliminate detectable traces of disease.

Dr. Caudle: For those of you who are just tuning in, you're listening to ReachMD. I'm Dr. Jennifer Caudle, and Dr. Daniel DeAngelo is here with me to talk about the value of minimal residual disease in patients with acute lymphoblastic leukemia. So, Dr. DeAngelo, now that we've discussed the basics of the immunotherapy BLINCYTO®, let's dive into some of the data. What can you tell us about the BLINCYTO® BLAST study results?

Dr. DeAngelo: The single-arm BLAST study included 86 MRD(+) patients in either first or second complete remission of ALL. And perhaps the most important takeaway is that BLINCYTO® converted 81 percent of these patients to an MRD(–) status.

Not only that, but the majority of patients who converted to MRD(–) status were able to proceed to a stem cell transplant.

Another impressive data point from the BLAST study was related to relapse-free survival, or RFS. There was a 4-times longer median RFS in patients who achieved MRD(–) status versus those patients who remained MRD(+) (23.6 vs 5.7 months). Of the patients in the Key Secondary Endpoint Full Analysis Set, 67% or (74 patients out of 110) proceeded to a hematopoietic stem cell transplant in continuous remission, which is a potential confounder. Therefore, the survival benefit cannot be isolated to BLINCYTO® treatment alone.

In addition, patients treated in first complete remission, or CR1, achieved a median RFS of 35.2 months, while patients treated in CR2 achieved a median RFS of 12.3 months.

Dr. Caudle: How did the patients in the BLAST study typically tolerate BLINCYTO®?

Dr. DeAngelo: In the BLAST study, the majority of the most common adverse events were mild to moderate. The most common adverse reactions (≥ 20%) in patients with MRD-positive B-cell precursor ALL treated with BLINCYTO® were pyrexia, infusion-related reactions, headache, infections (pathogen unspecified), tremor, and chills. Serious adverse reactions were reported in 61% of patients.

Dr. Caudle: Great, and thanks for breaking that down for us, Dr. DeAngelo. And maybe now you could walk us through the journey of a recent patient treated with BLINCYTO®? How was their experience on treatment? And what do you tell your patients to expect when they're on BLINCYTO®?

Dr. DeAngelo: Certainly. In fact, an example of a patient comes to mind. This is a patient who is a 45-year-old female who was diagnosed with B-cell precursor ALL. She completed induction and one cycle of consolidation chemotherapy and achieved a complete remission. However, when I conducted an MRD test using flow cytometry, she tested positive. To give her the best overall outcome, I decided to prescribe BLINCYTO® with the goal of achieving an MRD negative status prior to stem cell transplant. I told her that the

majority of the most common adverse reactions with BLINCYTO® are mild to moderate, and that we'd need to keep an eye out for cytokine release syndrome as well as neurologic toxicities.

I explained to my patient that although she achieved a complete remission, there was still a relatively small number of cancer cells in her bone marrow, as proven by the MRD test. Because of this, I told her BLINCYTO® could potentially eliminate the remaining detectable traces of cancer to give her a better chance for a cure with stem cell transplant.

After completing one cycle of BLINCTYO®, she achieved MRD negative status as measured by flow cytometry and is currently preparing for transplantation. She tolerated BLINCYTO® quite well and appreciated being able to receive the majority of her treatment at home. But as you know, all patients respond differently.

Dr. Caudle: And before we wrap up, do you have any insights for other HemOncs when it comes to MRD testing?

Dr. DeAngelo: I believe MRD testing is essential, but it needs to be done in a specific manner and in a laboratory that is capable of measuring MRD. Based on my clinical experience, it is important to reiterate that is the very first pull containing only two to three CCs of bone marrow aspirate should be used for MRD testing, and that the pathology lab must be able to differentiate between MRD analysis and routine immunophenotyping. It's also essential that at least one million events be assayed in order to attain an accurate result.

All of this is to say that a patient's MRD status is important. Its prognostic value is very exciting, and I think it is something that should be considered and used in treatment practices. Converting patients to MRD(–) status has been proven to lead to longer relapse-free survival and a prolonged survival. Achieving MRD negativity prior to transplant offers patients a better chance for long-term survival as compared to patients who remain MRD-positive. And lastly, for any listeners out there who would like to learn more about BLINCYTO® and the BLAST study results, I'd encourage them to visit www.blincyto.com for more information.

Dr. Caudle: Well with that, I want to thank Dr. Daniel DeAngelo for joining me today in discussing minimal residual disease with our ReachMD audience. It was great speaking with you, Dr. DeAngelo.

Dr. DeAngelo: Thank you very much, I really enjoyed the time.

Announcer: We would now like to cover important safety information for BLINCYTO®.

BLINCYTO® (blinatumomab) is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (or ALL) in first or second complete remission with minimal residual disease (or MRD) greater than or equal to 0.1% in adults and children.

This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Here is the IMPORTANT SAFETY INFORMATION for BLINCYTO®.

- Cytokine Release Syndrome (or CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® and treat with corticosteroids as recommended.
- Neurological toxicities, which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.
- BLINCYTO® is contraindicated in patients with a known hypersensitivity to blinatumomab or to any component of the product formulation.
- CRS, which may be life-threatening or fatal, occurred in 15% of patients with R/R ALL and in 7% of patients with MRD-positive ALL. The median time to onset of CRS is 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Closely monitor and advise patients to contact their healthcare professional for signs and symptoms of serious adverse events such as fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (or ALT), increased aspartate aminotransferase (or AST), increased total bilirubin (or TBILI), and disseminated intravascular coagulation. The manifestations of CRS after treatment with BLINCYTO® overlap with those of infusion reactions, capillary leak syndrome, and hemophagocytic histiocytosis/macrophage activation syndrome. If severe CRS occurs, interrupt BLINCYTO® until CRS resolves. Discontinue permanently if life-threatening CRS occurs. Administer corticosteroids for severe or life-threatening CRS.
- Approximately 65% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. The median time to the first event was within the first 2 weeks of BLINCYTO® treatment and the majority of events resolved. The most common manifestations of neurological toxicity (≥ 10%) were headache and tremor. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 13% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. Monitor patients for signs or symptoms and interrupt or discontinue BLINCYTO® as outlined in the

PI.

- Approximately 25% of patients receiving BLINCYTO® in clinical trials experienced serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections, some of which were life-threatening or fatal. Administer prophylactic antibiotics and employ surveillance testing as appropriate during treatment. Monitor patients for signs or symptoms of infection and treat appropriately, including interruption or discontinuation of BLINCYTO® as needed.
- Tumor Lysis Syndrome (or TLS), which may be life-threatening or fatal, has been observed. Preventive measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used during BLINCYTO® treatment. Monitor patients for signs and symptoms of TLS and interrupt or discontinue BLINCYTO® as needed to manage these events.
- Neutropenia and Febrile Neutropenia, including life-threatening cases, have been observed. Monitor appropriate laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO® infusion and interrupt BLINCYTO® if prolonged neutropenia occurs.
- Due to the possibility of neurological events, including seizures, patients receiving BLINCYTO® are at risk for loss of consciousness, and should be advised against driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO® is being administered.
- Transient elevations in liver enzymes have been associated with BLINCYTO® treatment with a median time to onset of 3 days. In patients receiving BLINCYTO®, although the majority of these events were observed in the setting of CRS, some cases of elevated liver enzymes were observed outside the setting of CRS, with a median time to onset of 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients. Monitor ALT, AST, gamma-glutamyl transferase, and TBILI prior to the start of and during BLINCYTO® treatment. BLINCYTO® treatment should be interrupted if transaminases rise to > 5 times the upper limit of normal (or ULN) or if TBILI rises to > 3 times ULN.
- Fatal pancreatitis has been reported in patients receiving BLINCYTO® in combination with dexamethasone in clinical trials and the post-marketing setting. Evaluate patients who develop signs and symptoms of pancreatitis and interrupt or discontinue BLINCYTO® and dexamethasone as needed.
- Although the clinical significance is unknown, cranial magnetic resonance imaging changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO®, especially in patients previously treated with cranial irradiation and antileukemic chemotherapy.
- Preparation and administration errors have occurred with BLINCYTO® treatment. Follow instructions for preparation (including admixing) and administration in the PI strictly to minimize medication errors (including underdose and overdose).
- Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO® treatment, during treatment, and until immune recovery following the last cycle of BLINCYTO®.
- Serious and fatal adverse reactions including “gasping syndrome,” which is characterized by central nervous system depression, metabolic acidosis, and gasping respirations, can occur in neonates and infants treated with benzyl alcohol-preserved drugs including BLINCYTO® (with preservative). When prescribing BLINCYTO® (with preservative) for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO® (with preservative) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known. Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO® solution for infusion with preservative contain benzyl alcohol and are not recommended for use in any patients weighing < 22 kg.
- The most common adverse reactions (≥ 20%) in clinical trial experience of patients with MRD-positive B-cell precursor ALL (from the BLAST Study) treated with BLINCYTO® were pyrexia (91%), infusion-related reactions (77%), headache (39%), infections (pathogen unspecified [39%]), tremor (31%), and chills (28%). Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection.
- Adverse reactions that were observed more frequently (≥ 10%) in the pediatric population compared to the adults with relapsed or refractory B-cell precursor ALL were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).
- In pediatric patients less than 2 years old (infants), the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different; the only event terms reported were agitation, headache, insomnia, somnolence, and irritability. Infants also had an increased incidence of hypokalemia (50%) compared to other pediatric age cohorts (15-20%) or adults (17%).

Announcer: This program was brought to you by Amgen. To learn more about BLINCYTO® and the BLAST study results, you can visit www.blincyto.com that’s www.blincyto.com. This is ReachMD. Be Part of the Knowledge.