Transcript Details

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Frontline Consolidation in B-ALL: Expert Insights on the Role of Blinatumomab

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are refined as often as new data and information become available. Please note, the NCCN Content referenced in this session may have updated since the time and date of this original recording.

Here's your host, Dr. Charles Turck.

Dr. Logan was not compensated for his participation.

Dr. Turck:
Welcome to ReachMD. I'm Dr. Charles Turck, and today, we'll be discussing key data, including the Phase III E1910 trial, on blinatumomab in frontline consolidation for Philadelphia chromosome-negative B-lineage acute lymphoblastic leukemia, or B-ALL. We'll be hearing from an expert on how this data with blinatumomab is impacting the National Comprehensive Cancer Network, or NCCN, Guidelines® and clinical practice.

Joining me in our discussion is Dr. Aaron Logan, who's a Professor of Clinical Medicine in the Division of Hematology/Oncology and Director of the Hematologic Malignancies Tissue Bank at UCSF. Dr. Logan, welcome to the program.

Dr. Logan:
Thank you so much. It's a great pleasure to be here to talk with you about this tremendous advance in the care of ALL for our patients.

Dr. Turck:
Well, before we get started, let's take a moment to hear the Indication and Boxed Warnings for blinatumomab.

ReachMD Announcer:
BLINCYTO® (blinatumomab) HCP Important Safety Information

INDICATIONS
BLINCYTO® (blinatumomab) is indicated for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adult and pediatric patients one month and older with:

- Philadelphia chromosome-negative disease in the consolidation phase of multiphase chemotherapy
- Minimal residual disease (MRD) greater than or equal to 0.1% in first or second complete remission
- Relapsed or refractory disease

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- **Cytokine Release Syndrome (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, including immune effector cell-associated neurotoxicity syndrome (ICANS) which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**

Stay tuned for additional Important Safety Information later during this podcast.

Dr. Turck:
Now that we've heard that important safety information, let's start our discussion with some background on the E1910 Phase III trial. This studied the addition of blinatumomab to consolidation chemotherapy in newly diagnosed patients with Philadelphia chromosome-negative B-ALL who were measurable residual disease-negative after induction chemotherapy. So with all that in mind, Dr. Logan, can you tell us more about this study?

Dr. Logan:
Despite the fact that ALL is a relatively rare disease with fewer than 7,000 people diagnosed each year in the US, over half of them children and young adults,[1,2] there's been a remarkable amount of progress in the management of this leukemia over the last many years.

Now in children, long-term survival rates already exceed 90 percent, but outcomes in adults have been lagging for quite a while.[3] One of the things the adult hematology world learned really well from pediatric studies was the importance of monitoring what we call MRD, short for measurable residual disease, previously known as minimal residual disease, which helps determine how well patients are responding to their therapy.[3,4]

In my view, a critical development in the field was the 2018 approval of blinatumomab, which is a CD19-directed bispecific T-cell engager, for treating MRD-positive B-ALL during the first and second remission.[5] Since then, many of my patients have received blinatumomab in this context.

The E1910 study is the next evolution in the utilization of this important immunotherapy for B-ALL by moving it into front-line consolidation. The E1910 study sought to address whether administering blinatumomab was beneficial to patients who achieved remission and were MRD negative at the level of 0.01 percent, or 10 to the minus four or another way of saying that is one leukemia cell out of ten thousand nucleated cells, using a testing methodology called flow cytometry.[6]

So this was a phase III randomized controlled trial in which patients aged 30 to 70 years with newly diagnosed Philadelphia-negative B-ALL received two cycles of induction as needed followed by one cycle of CNS intensification chemotherapy, and then they were randomized to one of two study groups.[6]

One of the groups of 112 patients received two cycles of blinatumomab followed by four more cycles of chemotherapy and two more cycles of blinatumomab. For those unfamiliar with the study, it can be noted that blinatumomab cycles were integrated with the chemotherapy rather than sequential. Meanwhile, the other group of 112 patients just received the additional four cycles of chemotherapy. Everyone in both groups then went on to receive what we call POMP maintenance for a total of two and a half years after remission was achieved. The E1910 primary endpoint was the overall survival in patients who received blinatumomab after the initial chemotherapy versus chemotherapy alone.[6]

Initially, the study also randomized MRD-positive patients, but when blinatumomab was approved for treatment of MRD-positive ALL, the study protocol was changed so that all MRD-positive patients could then receive blinatumomab.[6]

It's important to note that MRD was assessed centrally using a standardized six-color flow cytometry assay, with MRD-negative defined as less than 0.01 percent leukemic cells in the bone marrow.[6] The MRD tests were performed at a laboratory site using assays that have not been analytically validated by the FDA.

Dr. Turck:
That's important context for this study, thanks. And what were the results from E1910?

Dr. Logan:
Well, the pivotal findings from the E1910 study were that the MRD-negative patients who received blinatumomab as part of their frontline consolidation experienced 84.8 percent overall survival at three years, which was significantly higher than the 69 percent in the chemo-alone arm, which gave a hazard ratio of 0.42 with a significant P value.[5] The median overall survival was not reached in the blinatumomab arm and was 71 months in the chemo arm.[7] So what this means is that treatment with frontline blinatumomab was associated with a 58 percent reduction in death from any cause compared to chemotherapy consolidation alone.[8]

Additionally, and very importantly, the median relapse-free survival was not reached in the blinatumomab arm and was less than two years in the chemotherapy-only arm, showing an improvement in relapse-free survival for this disease in adult patients.[6,7]

Also, no new safety concerns with the use of blinatumomab were identified in E1910.[6,9]

Fatal adverse reactions occurred in two percent of patients during blinatumomab cycles and were associated with infection and coagulopathy. Permanent discontinuation of blinatumomab due to adverse reaction occurred in two percent of patients while dose interruptions occurred in 5 percent of patients. The rate of grade three and four cytokine release syndrome events was four percent when blinatumomab was used in frontline consolidation.[5]

The most common adverse events during consolidation cycles in the blinatumomab arm, occurring in at least 20 percent of patients, were various cytopenias - and that would include neutropenia, lymphopenia, anemia, thrombocytopenia, but also headaches, infections, nausea, diarrhea, musculoskeletal pain, and tremors.[5]

On the basis of the E1910 results, the *National Comprehensive Cancer Network® (NCCN®) now* recommends that blinatumomab be incorporated into consolidation therapy for patients with B-ALL, regardless of the MRD status.[10]

Dr. Turck:
Thanks for walking us through the E1910 results, Dr. Logan. Now can you share your thoughts on these findings, and how they've impacted your clinical practice?

Dr. Logan:
Well to me, it would not be an exaggeration to say that this is a practice-changing study given the benefit for patients when they receive blinatumomab consolidation, even if they achieve an MRD-negative remission with initial chemotherapy. Indeed, I think that MRD below the level of 0.01 percent is meaningful as a predictor of clinical outcomes and that providing an immunological consolidation with blinatumomab for patients is important for maximizing the likelihood of long-term relapse-free and overall survival. I think one of the important points to note about E1910 was that only 60 percent of the patients got to the randomization of blinatumomab versus chemotherapy, which I think indicates that the initial BFM backbone used may not have been optimal due to toxicities and some patients experiencing early progression.[6,11,12]

Due to that, in my practice, we have opted to use the hyper-CVAD regimen with blinatumomab with some minor modifications based on favorable published data. This regimen includes four cycles of chemotherapy and four cycles of blinatumomab in consolidation and has proven to be manageable, with our patients so far, experiencing really great outcomes.[6]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Aaron Logan about blinatumomab in consolidation for adult patients with Philadelphia-negative B-ALL who are MRD-negative.

Now let's turn to the NCCN Guidelines for ALL. How have these guidelines for adult patients evolved with the E1910 study results and other key data of blinatumomab in frontline consolidation?

Dr. Logan:
The NCCN Guidelines have made very important changes in the recommendations regarding the management of ALL in the past years. First amongst those, I think, is reinforcing the importance of monitoring MRD in all patients with this leukemia and making appropriate therapeutic changes, when indicated—for instance, giving blinatumomab for MRD-positive ALL in recent years.[10] With the ECOG 1910 study and including the hyper-CVAD blinatumomab as a potential option,[10] NCCN decided the preponderance of data suggests that blinatumomab is appropriate consolidation therapy for patients with Philadelphia-negative B-ALL as the FDA has approved blinatumomab for this indication agnostic of chemotherapy backbone based on the E1910 regimen.[10]

I think it's appropriate for each institution to decide whether they want to implement the E1910 backbone, use hyper-CVAD plus blinatumomab, or perhaps incorporate blinatumomab consolidation in to other regimens. For centers that for one reason or another cannot administer blinatumomab, I think it is extremely important now for them to refer patients to a center that *can* administer blinatumomab consolidation as early as possible. What I've noticed over the years, though, is that more and more centers are gaining the ability to administer blinatumomab, and I hope to see this continue to spread so that as many patients as possible can benefit from this therapy.

Dr. Turck:
And in your experience, Dr. Logan, are there practical considerations or logistical barriers to incorporating the NCCN Guidelines'

recommendations in your management of Philadelphia-negative B-ALL patients?

Dr. Logan:
Yes, I think so. Going back to what I previously mentioned, we had some concerns about the drop-out rate during the initial cycles of BFM-type therapy on E1910. Because of that, we opted to use hyper-CVAD plus blinatumomab, so the ability to adapt blinatumomab to any regimen for consolidation is really important, and I think alleviates barriers that might have existed with a more strict provision of specific regimens in which blinatumomab can be used for consolidation. That said, as with many therapies in oncology, there's not a one-size-fits-all approach, and patient-specific factors may come into play. We, for instance, require patients to have a caregiver during blinatumomab therapy to maximize safety. Maybe not all centers do that, but sometimes this can present a barrier. We also work very hard with patients and their friend and family network to secure caregivers when needed. Since we consider this a really critical component of the therapy now. And we want all patients who are eligible to be able to receive it.

Dr. Turck:
So with the E1910 study and NCCN Guidelines in mind, Dr. Logan, how do you manage a newly diagnosed adult with B-ALL, and does this vary by patient age, depth of MRD, or other factors?

Dr. Logan:
I think that's a great question. I do think there is still some room for debate regarding whether young adults up to the age of 40 warrant therapy on a BFM-type backbone containing PEG-asparaginase. At my center, we have opted to use hyper-CVAD plus blinatumomab in all adult patients, but we will of course be looking forward to additional data incorporating blinatumomab in other backbones.

So as it stands today, the first step in choosing therapy for an adult with B-ALL is to determine their Philadelphia chromosome status, and if they are Ph-negative, they will receive hyper-CVAD with blinatumomab. We monitor MRD using the ClonoSEQ NGS assay at the end of induction and at other important timepoints, including following the second cycle of blinatumomab. Those who remain MRD-positive will go on to allogeneic transplant, potentially with other therapy as a bridge, depending on the MRD level.

Dr. Turck:
And where do you see the overall treatment landscape for B-ALL headed in terms of areas of ongoing or future research?

Dr. Logan:
All of us who treat patients would like to see, in the future, that we achieve the best possible outcomes but also try and decrease the use of conventional cytotoxic chemotherapy and the typically very long duration of therapy that's needed for ALL.[13] Right now, patients have medical appointments and monthly treatments that continue for several years.[13] It would be great to eliminate as much of this burden for patients as possible. I think the optimal approach is yet to be determined, but there are several clinical studies trying to address just this.

Dr. Turck:
Now as we come to the end of our program, Dr. Logan, are there any key takeaways you'd like to leave with our audience today?

Dr. Logan:
Absolutely, based on the data we have discussed, adult patients with Philadelphia-negative B-ALL achieving MRD-negative remission, as defined as less than 0.01 percent leukemia cells in the bone marrow, have significantly improved overall survival with the use of blinatumomab in frontline consolidation.[6]

The E1910 study also provided strong data that MRD less than 0.01 percent is clinically meaningful and associated with relapse, especially in patients who do not receive blinatumomab in consolidation.[6] And I think this reinforces the need for assessment of measurable residual disease using a high sensitivity test to give providers the best prognostic information about how their patients are responding to treatment and ultimately allows management decisions that can improve outcomes in adults with B-ALL.[6]

I think blinatumomab is essential immunologic consolidation for B-ALL patients, and using it can help provide favorable outcomes while potentially avoiding an allogeneic transplant.[6]

Dr. Turck:
Those are great insights for us to think on as we come to the end of today's program.

I want to thank my guest, Dr. Aaron Logan, for reviewing the data on blinatumomab in frontline consolidation for Philadelphia chromosome-negative B-lineage acute lymphoblastic leukemia and for also sharing insights into how he personally implements these findings into clinical practice.

Dr. Logan, it was great speaking with you today.

Dr. Logan:
And it was great talking with you as well. I hope this is helpful to your listeners, and I hope that patients can benefit from additional awareness of this advance.

Dr. Turck:
I'm Dr. Charles Turck.

And before we close, let's take a moment to review some Important Safety Information.

ReachMD Announcer:
Contraindications
BLINCYTO® is contraindicated in patients with a known hypersensitivity to blinatumomab or to any component of the product formulation.

Warnings and Precautions

- **Cytokine Release Syndrome (CRS):** CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. 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 (ALT), increased aspartate aminotransferase (AST), increased total bilirubin, and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO® overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). Using all of these terms to define CRS in clinical trials of BLINCYTO, CRS was reported in 15% of patients with R/R ALL, in 7% of patients with MRD-positive ALL, and in 16% of patients receiving BLINCYTO® cycles in the consolidation phase of therapy. If severe CRS occurs, interrupt BLINCYTO® until CRS resolves. Discontinue BLINCYTO® permanently if life-threatening CRS occurs. Administer corticosteroids for severe or life-threatening CRS.

- **Neurological Toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome:** BLINCYTO® can cause serious or life-threatening neurologic toxicity, including ICANS. The incidence of neurologic toxicities in clinical trials was approximately 65%. The median time to the first event was within the first 2 weeks of BLINCYTO® treatment. The most common (≥ 10%) manifestations of neurological toxicity were headache and tremor. Grade 3 or higher 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. The majority of neurologic toxicities resolved following interruption of BLINCYTO®, but some resulted in treatment discontinuation.

  The incidence of signs and symptoms consistent with ICANS in clinical trials was 7.5%. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. There is limited experience with BLINCYTO® in patients with active ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical studies. Patients with Down Syndrome may have a higher risk of seizures with BLINCYTO® therapy; consider seizure prophylaxis prior to initiation of BLINCYTO® for these patients.
  Monitor patients for signs and symptoms of neurological toxicities, including ICANS, and interrupt or discontinue BLINCYTO® and/or treat with corticosteroids as outlined in the PI. Advise outpatients to contact their healthcare professional if they develop signs or symptoms of neurological toxicities.

- **Infections:** 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 (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.

- **Effects on Ability to Drive and Use Machines:** Due to the possibility of neurological events, including seizures and ICANS, 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.

- **Elevated Liver Enzymes:** 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 total blood bilirubin 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 (ULN) or if total bilirubin rises to > 3 times ULN.

- **Pancreatitis:** 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.

- **Leukoencephalopathy:** Although the clinical significance is unknown, cranial magnetic resonance imaging (MRI) 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).

- **Immunization:** 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 last cycle of BLINCYTO®.

- **Benzyl Alcohol Toxicity in Neonates:** Serious adverse reactions, including fatal reactions and the “gasping syndrome,” have been reported in very low birth weight (VLBW) neonates born weighing less than 1500 g, and early preterm neonates (infants born less than 34 weeks gestational age) who received intravenous drugs containing benzyl alcohol as a preservative. Early preterm VLBW neonates may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

  Use the preservative-free preparations of BLINCYTO® where possible in neonates. When prescribing BLINCYTO® (with preservative) for neonatal patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO® (with preservative), other products containing benzyl alcohol or other excipients (e.g., ethanol, propylene glycol) which compete with benzyl alcohol for the same metabolic pathway.

  Monitor neonatal patients receiving BLINCYTO® (with preservative) for new or worsening metabolic acidosis. The minimum amount of benzyl alcohol at which serious adverse reactions may occur in neonates is not known. The BLINCYTO® 7-Day bag (with preservative) contains 7.4 mg of benzyl alcohol per mL

- **Embryo-Fetal Toxicity:** Based on its mechanism of action, BLINCYTO® may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with BLINCYTO® and for 48 hours after the last dose.

Adverse Reactions

- The safety of BLINCYTO® in adult and pediatric patients one month and older with MRD-positive B-cell precursor ALL (n=137), relapsed or refractory B-cell precursor ALL (n=267), and Philadelphia chromosome-negative B cell precursor ALL in consolidation (n=165) was evaluated in clinical studies. The most common adverse reactions (≥ 20%) to BLINCYTO® in this pooled population were pyrexia, infusion-related reactions, headache, infection, musculoskeletal pain, neutropenia, nausea, anemia, thrombocytopenia, and diarrhea.

Dosage and Administration Guidelines

- BLINCYTO® is administered as a continuous intravenous infusion at a constant flow rate using an infusion pump which should be programmable, lockable, non-elastomeric, and have an alarm.
- It is very important that the instructions for preparation (including admixing) and administration provided in the full Prescribing Information are strictly followed to minimize medication errors (including underdose and overdose).

Please see accompanying BLINCYTO® full Prescribing Information, including BOXED WARNINGS on this program's landing page or BLINCYTOHCP.com.

ReachMD Announcer:
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