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ASH 2024:

Key Highlights from the American Society of Hematology 66th Annual Meeting and Exposition

The American Society of Hematology (ASH) Annual Meeting is a cornerstone event for advancements in hematology, showcasing the latest breakthroughs in clinical and translational research. Last year's meeting was particularly exciting, featuring an array of updates across hematologic oncology, gene therapy, and rare disorders. For InspiroGene by McKesson, ASH 2024 showcased both the cutting-edge scientific advancements being made and the tangible impact that these innovations have on patient outcomes.

In this series, we dive into some of the most impactful insights and takeaways from the conference, highlighting key research findings and emerging trends that are poised to shape the future of cell and gene therapy. This first installment covers important panel discussions centered on CAR T-cell therapy for cancers, particularly lymphomas and multiple myeloma, as well as a focus on the considerations and strategies for administering therapy in the outpatient setting.

Emerging Trends and Controversies in CAR T-Cell Therapy

Advancements and Challenges in CAR T-Cell Therapy for Lymphomas

Various panel discussions on CAR T-cell therapy highlighted significant advancements and controversies in the treatment of diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL).[1,2]

In the third-line treatment setting for DLBCL, the approvals of Yescarta, Breyanzi, and Kymriah are supported by key trials—ZUMA-1, TRANSCEND, and JULIET, respectively—demonstrating durable benefits with 5-year overall survival rates of 42.6% for Yescarta and 38.1% for Breyanzi. However, a major point of debate at ASH was the sequencing of CAR T-cell therapy and bispecific T-cell engagers (BiTEs) such as Columvi and Epkinly. Overall, the panelists seemed to strongly favor using CAR T before BiTEs mainly due to CAR T's demonstrated curative potential and longer follow-up data. Additionally, it was thought that using BiTES prior to CAR T might also lead to immune resistance or T cell exhaustion, however emerging data from the French DESCARTES registry suggest that BiTEs may not compromise CAR T efficacy if used first. This divergence highlights the need for more randomized studies to guide sequencing decisions.

In the second-line setting for DLBCL, both Yescarta and Breyanzi have shown superior outcomes compared to standard-of-care chemotherapy,

with overall response rates (ORRs) of 83% and 87%, respectively. Kymriah, however, failed to show survival benefit in the BELINDA trial. Overall, expert panels emphasized that outcomes improve when CAR T is used earlier, with better complete response rates and OS in the second-line setting compared to third-line use.

In FL, all three approved CAR T therapies—Yescarta, Breyanzi, and Kymriah — have demonstrated strong outcomes in relapsed or refractory settings, with Yescarta showing the longest follow-up data. However, expert panelists noted that toxicity remains a differentiating factor; Yescarta's rates of neurotoxicity and cytokine release syndrome (CRS), are comparatively higher than Breyanzi and Kymriah, making toxicity management a focal point of FL treatment strategies. In MCL, discussions described Tecartus and Breyanzi as having comparable response rates but differences in toxicity and overall survival outcomes. Panel discussions highlighted Tecartus's higher CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) rates, while Breyanzi offered a more tolerable safety profile but shorter median overall survival.

Treatment selection was another key focal point, with discussions to consider Breyanzi in frail patients with comorbidities due to lower toxicity potential and Yescarta for aggressive disease because of its strong efficacy profile and comparatively quicker manufacturing timeline. Additionally, toxicity management remains a challenge, especially with Yescarta, which has shown higher rates of CRS and ICANS. However, the panelists noted improved recognition and earlier intervention have mitigated these risks over time.

The pipeline of next-generation therapies was another key topic of discussion, with advances in rapid manufacturing and novel constructs like anti-CD22 CAR T therapies offering new options for patients who fail anti-CD19 CAR T. Allogeneic CAR T products, such as Allo-501A, have shown early promise with favorable safety profiles and no graft versus host disease (GVHD), potentially addressing access and scalability issues.

Looking ahead, trials exploring CAR T in first-line settings, such as Yescarta in ZUMA-12, offer a glimpse into the potential for high-risk patients. The field continues to grapple with balancing efficacy, toxicity, and accessibility, bringing to light the dynamic and rapidly evolving landscape of hematologic oncology.

Considerations in Multiple Myeloma

CAR T-cell therapy in multiple myeloma (MM) emerged as a key focus in various ASH discussions, with exciting data highlighting its potential in earlier treatment lines.[3,4] FDA-approved therapies such as Abecma and Carvykti target BCMA and have demonstrated improved outcomes when used earlier, as shown in trials such as KarMMa-3 and CARTITUDE-4. Panel speakers noted that early use preserves T-cell fitness, improves efficacy, and offers longer treatment-free remissions, particularly benefiting patients with fewer comorbidities.

Expert panelists agreed that bridging therapy is essential during the manufacturing of CAR T-cell product, with a focus on maintaining disease control. However, sequencing remains a topic of debate. Experts emphasized avoiding BCMA-targeting bispecific drugs prior to CAR T-cell therapy to prevent suboptimal responses, instead recommending other treatment options, including non-BCMA agents such as GPRC5D-targeted therapies.

The safety and toxicity profile of BCMA-targeted CAR T-cell therapy was another major topic of discussion. CRS and ICANS are most likely to occur within the first 30 days of treatment, with CRS typically occurring within 24 hours for Abecma and later (day 7) for Carvykti. Neurotoxicities and cytopenias were also noted as common delayed toxicities, with some patients experiencing persistent cytopenias for three months or more. Lastly, infections remain a significant risk, necessitating prophylactic treatments.

Real-world data highlighted access challenges, as only 10% of eligible patients receive CAR T-cell therapy due to logistical, socioeconomic, and provider-related barriers. In addition to access issues, long-term management of delayed toxicities adds another layer of complexity. Effective care requires seamless coordination between CAR T-cell therapy centers and community providers to ensure patients receive comprehensive support. Despite these hurdles, ongoing trials and innovations are expanding CAR T's role in MM, with the potential to transform outcomes for a broader range of patients.

Making Outpatient CAR T-Cell Therapy a Reality

A dedicated session at ASH focused on the requirements and strategies to successfully implement outpatient CAR T-cell therapy.[5] The discussion centered around key considerations, including:

- Institutional Infrastructure: Establishing outpatient programs requires close coordination between oncology teams, infusion centers, and emergency departments. Dedicated staff trained in monitoring and rapidly managing CAR T-specific toxicities, such as CRS and ICANS, is essential.

Patient Selection: Identifying appropriate patients is critical. Candidates must be medically stable, reside near the treatment facility for an extended period of time, and have reliable caregivers. Additionally, patients and their caregivers must be educated on the expectations of CAR T-cell therapy. The provider team, which includes the physician, nurse, social worker, and pharmacist, must be coordinated in their approach to patient education and support. Consistent monitoring of patient vitals, whether through wearable technology or caregiver assistance, is crucial to ensure safe outcomes.

- Logistical Planning: Clear protocols for outpatient management, including same-day access to inpatient care if required, are necessary. In addition, partnerships with local health systems can help streamline transitions if complications arise.

Speakers noted that the outpatient model not only reduces the burden on hospital resources but also improves patient quality of life by allowing them to recover in the comfort of their homes. However, it requires significant investment in training, logistics, and patient support systems to ensure safety and efficacy.

Expanded Potential for CAR T-Cell Therapies

Panels at ASH 2024 showcased the great potential for expanding indications, particularly for high-risk patients, as well as the need for making these therapies available to more patients, including transitioning treatments into outpatient settings, a critical step to improve access to care.

1. American Society of Hematology. Addressing Current Questions and Controversies Regarding the Role of CAR T-Cell Therapy and Bispecific Antibodies in the Management of Lymphoma - What Clinicians Want to Know. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.
2. American Society of Hematology. Show Me the Data: Pushing CAR T's Forward Across Lymphoid Malignancies... Accelerating Access in the Community and Treatment Strategies for the Road Ahead. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.
3. American Society of Hematology. A Step-by-Step Approach to CAR T-Cell Therapy for RRMM: From Bridging to Sequencing and Adverse Event Management. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.
4. American Society of Hematology. Bridging Gaps in Multiple Myeloma Care: A Community Oncologist's Guide to Navigating the Evolving Treatment Landscape. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.
5. American Society of Hematology. How I Treat: Adult Outpatient CAR T Therapy. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.