OUTPATIENT ADMINISTRATION OF BiTEs IN COMMUNITY ONCOLOGY CLINICS

EVOLVING PRACTICE, REAL-WORLD FEASIBILITY & FUTURE DIRECTIONS

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Bispecific T-Cell Engagers (BiTEs) are revolutionizing cancer immunotherapy by providing targeted and effective treatment options for patients who have exhausted traditional therapies.

A novel class of bispecific antibodies, BiTEs partner the cytotoxic power of a patient's own immune system, specifically T cells, to identify, bind to and eliminate previously unrecognizable cancer cells.

The current FDA-approved treatments to be discussed are used for the treatment of leukemia, lymphoma, lung cancer, multiple myeloma and rare forms of melanoma that previously lacked effective options. These therapies are not first-line treatments. BiTEs are indicated after two or more prior therapies have failed, offering a crucial treatment option for patients with relapsed or refractory disease.

BiTEs represent a transformative advancement in cancer immunotherapy. As the hematology and oncology landscape continues to evolve, outpatient delivery of BiTE therapies in the community setting will be paramount in expanding access and improving outcomes for patients with limited treatment options.

With strategic planning, multidisciplinary team training, caregiver education and appropriate patient selection, community administered BiTE programs can deliver powerful, life-extending therapies while minimizing and managing risk to enhance patients' quality of life.

MECHANISM AND PLACE IN THERAPY

BiTE therapy consists of T-cell engaging bispecific antibodies composed of two single-chain variable fragments linked together. One side binds to the CD3 receptor on a T cell and the other targets a specific antigen on the cancer cell, thus activating a T cell to recognize and destroy the tumor cell. BiTE serves as a bridge, bringing the immune system directly to the cancer.

Acting as a ready-made bridge confers many advantages over its comparator, chimeric antigen receptor T-cell (CAR-T) therapy. While both therapies use the immune system to target cancer, BiTE therapy distinguishes itself with its practicality and accessibility.

Unlike CAR-T, which involves a highly specialized process of extracting, reprogramming and reinfusing a patient's own

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T cells,[1] BiTE medications are procured much like other immunotherapies and are ready-to-use without a specialized treatment center or a protracted wait for treatment. This results in wider accessibility to patients and saves valuable time to treatment initiation.

With a similar but generally more manageable side-effect profile than CAR-T, BiTE therapy's advantages are impossible to ignore, making it a compelling treatment option with ever-growing indications.[2,3]

CLINICAL RISK LANDSCAPE: CRS, NEUROTOXICITY AND THE STEP-UP BARRIER

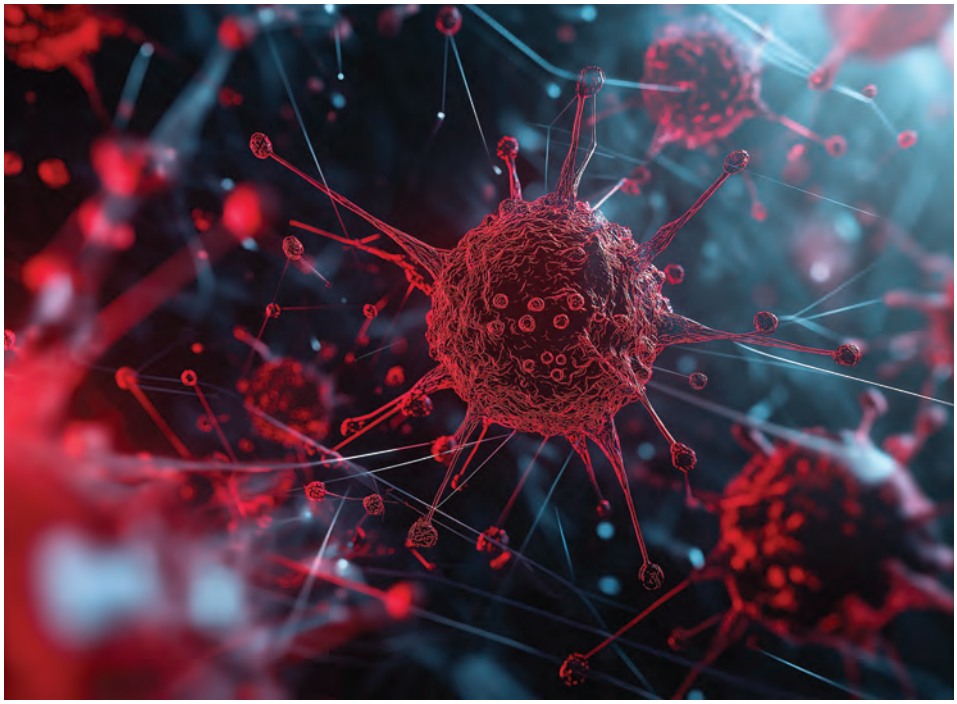
The clinical risk landscape of bispecific antibodies in oncology clinics is shaped by the unique safety challenges they bring. These therapies come with warnings related to cytokine release syndrome (CRS) and a type of neurotoxicity termed immune effector cell-associated neurotoxicity syndrome (ICANS).[4]

CRS is a systemic inflammatory response when the immune system is highly activated. This occurs as BiTEs redirect immune cells, especially T cells, to target cancer cells. These T cells release substantial amounts of cytokines that can cause widespread inflammation and result in a variety of issues from mild flu-like symptoms to life-threatening complications.[5]

Although CRS can have impacts throughout the body, the key symptoms are fever, hypoxia and hypotension.

ICANS, as well, is believed to be a result of cytokine release and the subsequent disruption of the blood brain barrier. Symptoms of ICANS can range from mild to severe. They can present as a headache or lethargy or, in more severe cases, seizures and even coma.[6]

To mitigate these toxicities, step-up dosing strategies have become standard. These introductory doses gradually escalate BiTE administration to cautiously expose patients to these immune-altering therapies and reduce the severity of immune-related toxicities.



A computer-generated image of targeted molecules engaging in a strategic assault on diseased cells.

While this slow dose escalation is paramount for patient safety, this requirement poses logistical burdens that could limit access for patients, particularly those in community or rural settings. These challenges include but are not limited to extended patient monitoring and increased healthcare resource utilization.

REAL-WORLD ADOPTION BARRIERS IN COMMUNITY ONCOLOGY

While initially administered exclusively in the inpatient setting due to the risk of significant toxicities, there is a growing impetus to move BiTE therapy to the community oncology infusion setting. This transition is designed to promote enhanced patient convenience, improved quality of life and more effective allocation of healthcare resources.

However, realizing this potential requires navigating significant real-world barriers, including hospital dependence for monitoring, payer complexities and the need for seamless care coordination.

Hospital dependence and effective safety monitoring, especially with the risk of severe and potentially life-threatening toxicities — primarily CRS and ICANS — pose the most critical barriers to overcome. Unlike traditional chemotherapy, the risks of CRS or ICANS are not limited to the infusion time, but may manifest hours or even days after the administration of BiTE therapy.[7]

Several strategies are necessary for the successful implementation of BiTE therapy in a community oncology setting. These strategies encompass tools for patient self-monitoring at home, multidisciplinary-driven clinic protocols for symptom management including dedicated remote patient monitoring, and an interprofessional team collaborating with local hospitals for observation or in response to emergent medical needs.

As community oncology practices strive to create a "hospital-at-home" level of safety when initiating BiTE therapy, it is imperative for the clinical team to strengthen care coordination with local hospitals. This is necessary regardless of whether the community practice will administer the BiTE therapy or admit patients to the hospital for a portion of the observation period. Establishing

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formal protocols and hand-off tools to manage BiTE-related toxicities creates a foundation for a cohesive and collaborative care environment.

Additionally, overcoming payer challenges for BiTE cell therapy requires a proactive payer engagement strategy that includes a comprehensive financial navigation team. Enabling this team to secure billing codes, apply appropriate modifiers and assess major payer reimbursement models before starting patients on bispecific therapy ensures program sustainability.[8]

Finally, the financial team is encouraged to connect with all patient assistance programs and foundations offered by the practice and drug manufacturer. This includes obtaining prior authorizations for the symptom management associated with CRS and ICANS. By performing these actions, the clinical financial team can help mitigate any financial toxicities for both patients and practice.

THE AON MODEL: A STRATEGIC APPROACH TO COMMUNITY ONCOLOGY BITE THERAPY

Despite the challenges of administering BiTE therapy in the community oncology setting, the American Oncology Network (AON) is committed to expanding access to this groundbreaking therapy to patients throughout the network.

To expand access, AON developed an all outpatient step up dosing protocol for patients to receive initiation doses without the need to be admitted to a hospital or academic setting for treatment or observation.

Because this protocol deviated from prescribing information that utilizes inpatient administration and observation, a new standard operating procedure (SOP) was created for the network. A multidisciplinary team of physician champions, pharmacists, nursing directors and financial counselors convened to discuss the logistics of developing a community oncology-based protocol.

With the right infrastructure, training and patient selection, bispecific antibody therapy can shift from a complex inpatient intervention to a safe, accessible and patient-centered community oncology standard of cancer care.

The team identified three key differences between community oncology and inpatient step-up dosing.

The differences were that:

- Patients need to be able to self-monitor for signs and symptoms of CRS and ICANS;
- Providers need access to resources for treating any adverse events; and
- Community-based clinics need access to prophylactic tocilizumab.

The main challenge was to develop a monitoring plan for CRS for the first 24 to 48 hours after receiving step-up dosing for patients and their caregivers to perform at home safely and reliably.

Patients receive a self-monitoring kit that includes a blood pressure cuff, a pulse oximeter and a thermometer. Patients must receive this kit prior to starting the community-based step-up protocol and the patient and primary caregiver must receive education from a nurse or advance practice practitioner on how to effectively use the kit's contents.

In addition to the self-monitoring kit, patients are given a medical bracelet that identifies them as a patient receiving step up dosing with bispecific therapy. The bracelet includes a QR code that can be scanned by any practitioner in an emergency. The QR code directs the provider to an AON sponsored website that has easily accessible information on how to manage CRS and ICANS.

The third key component of the community oncology model includes the use of prophylactic tocilizumab. Prophylactic tocilizumab is added to the flowsheet in the electronic medical record to be used at the physician's discretion. Additionally, clinics that utilize the outpatient step up protocol must maintain tocilizumab on hand in the pharmacy for the treatment of CRS.

Once the SOP was finalized, a comprehensive training plan was created. This training reviews the details of the community-based BiTE therapy SOP. Clinics across the network initiating the protocol receive training from a regional clinical pharmacist. The training reviews the responsibilities of each department within the practice to ensure the successful implementation of the community oncology bispecific program. This includes, but is not limited to providers, nurses, pharmacy staff and financial staff.

A Bispecific T-Cell Engager Preparedness checklist was created that includes criteria for patient and clinic eligibility to begin the BiTE program. Completion of the training and checklist ensures clinics and their patients are prepared for success upon program initiation.

Another key component is early pharmacist awareness and intervention. To support this, the pharmacy informatics team developed an Electronic Medical Record alert within the community-only BiTE therapy flow sheet.

When a physician places an order, the system automatically generates a consultation for the regional clinical pharmacist and sends an alert email. The pharmacist then collaborates with the provider and clinic team, reviews eligibility criteria for inclusion in the outpatient program, and ensures coordination of the patient self-monitoring kit.

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In addition, the pharmacist provides guidance to physicians, nurses and pharmacy technicians on step-up dosing preparation, administration, tocilizumab prophylaxis and management of adverse events.

KEY LESSONS LEARNED

Implementing community oncology administered BiTE therapy across the AON Network has offered several key lessons that continue to guide and refine best practices.

Most notably, effective toxicity management for CRS and ICANS remains the cornerstone of safe and successful treatment. Implementing structured protocols including patient education, premedication strategies, standardized triage pathways and strong interdisciplinary coordination has proven essential in maintaining treatment continuity and minimizing complications.

Pharmacists have played an essential role in developing and supporting these efforts by bringing important expertise that strengthens the overall process. Additionally, given the complexity of BiTE therapy, pharmacist-led interdisciplinary training has emerged as a critical component of community implementation.

A comprehensive, pharmacist-led education program ensures that all team members — including physicians, nurses, pharmacists and advanced practice providers — have a consistent understanding of treatment protocols, triage procedures and toxicity management strategies.

In parallel, patient selection has been identified as a key factor in community administration success. Risk stratification supports clinical decision-making by identifying patients best suited for treatment outside the hospital. This thorough assessment of each patient's and caregiver's ability to adhere to monitoring and symptom-reporting requirements further enhances safety.

Collectively, structured toxicity management protocols, pharmacist-led interdisciplinary training and careful patient selection have enhanced the feasibility and safety of delivering BiTE therapy in the community oncology setting.

FUTURE DIRECTIONS AND EVIDENCE GAPS

While early experience both within and outside our network supports the feasibility and safety of community-based bispecific therapy administration, including outpatient administration of step-up dosing, significant questions remain.[9,10]

Long-term outcomes, real-world safety in diverse populations and patient-reported quality of life require further study and will impact patient selection for a community-based approach.

Economic analyses evaluating both direct and indirect costs, as well as reimbursement differences across practice settings, will be important to ensure sustainable programs.

Successful expansion of outpatient bispecific programs will depend on reproducible and adaptable processes. Key enablers include standardized triage and monitoring protocols and consistent staff training.[11]

Variation in infrastructure, staffing and available community resources will require implementation strategies specific to each program. Sharing best practices and operational playbooks between health systems could accelerate safe and efficient scaling of outpatient bispecific therapy administration.

Various digital health solutions offer a path to extend patient monitoring beyond the hospital and clinic settings.[12] Telehealth visits, wearable vital sign sensors and application-based symptom reporting could enable earlier detection of CRS, neurotoxicity or other adverse events. Integration with the electronic medical record and automated alert systems could further enhance the patient-specific monitoring plan.

However, evidence supporting the clinical utility, patient adherence and cost-effectiveness of these innovative technologies, especially in the monitoring of patients on bispecific therapies, has yet to be published, and reimbursement issues may inhibit implementation.

The role of bispecific therapies is rapidly evolving, with ongoing trials investigating use in earlier lines of therapy, including front-line settings, across many indications.[13,14]

Earlier introduction may offer greater disease control and potentially improved survival, but involves less heavily pretreated patients with different support needs. Consequently, community oncology workflows, eligibility criteria and monitoring intensity will need to adapt as the role of bispecific therapy evolves.

The expanding pipeline of bispecific agents with diverse targets, improved tolerability, differing adverse effect profiles and novel dosing schedules is poised to reshape the administration of these agents in the community setting. Strategic planning, flexible infrastructure, and ongoing clinical and staff education will be essential to keep pace with these advances.

By addressing current evidence gaps, leveraging technology and preparing for a rapidly evolving therapeutic landscape, community oncology practices can position themselves to deliver safe, efficient, patient-centered care with these novel therapies.

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