A Multidisciplinary Approach to Standardizing Processes for Blinatumomab Administration

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Blinatumomab (Blincyto®) has received accelerated approval for treatment of relapsed or refractory acute lymphoblastic leukemia. This article describes the authors’ experience with a multidisciplinary collaboration among nursing, pharmacy, prescribers, and support staff, which has proven to be key for safe administration. The approach can be applied to other institutions planning to use blinatumomab.

At a Glance
- Blinatumomab is a therapy with many complexities regarding preparation, administration, monitoring, and coordination of care, which may pose challenges for successful implementation.
- Institutional blinatumomab guidelines and order sets serve as essential resources for the multidisciplinary team throughout the treatment process.
- A collaborative approach with a multidisciplinary team is needed for the safe administration of blinatumomab.

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Acute lymphoblastic leukemia (ALL) is a rare and often fatal cancer, with an estimated 6,590 new cases and 1,430 deaths in the United States in 2016 (American Cancer Society, 2016). ALL is most common in children and adolescents, with the majority of cases diagnosed in people younger than age 20 years. An estimated 42% of cases are diagnosed after age 20 years (National Cancer Institute, 2016).

The treatment of adults with ALL remains a challenge, and the success seen in pediatric patients is, unfortunately, not paralleled in the adult population. With currently available induction therapies, complete remission (CR) rates for newly diagnosed adult patients with ALL range from 74%–93%, depending on age and risk stratification (Bassan & Hoelzer, 2011; Fielding et al., 2007; Gökgübet & Hoelzer, 2009; Kantarjian et al., 2004; Oriol et al., 2010). Despite the high rates of CR, long-term disease-free survival is only achieved in about 40% of patients because of the high occurrence of relapse, which is observed in about 50% of patients (Fielding et al., 2007; Kantarjian et al., 2004; Oriol et al., 2010). Second remission (CR2) can be achieved in some cases; however, post-relapse treatment approaches rarely result in long-term survival. Studies have shown CR2 rates to be 42%–45% with conventional salvage combination chemotherapy regimens (Bassan & Hoelzer, 2011; Oriol et al., 2010). The post-relapse five-year overall survival rate is 4%–23% and is most often attained in patients who undergo hematopoietic stem cell transplantation (HSCT) (Fielding et al., 2007).

Blinatumomab

Obtaining a CR is an essential first step to undergoing successful HSCT (Fielding et al., 2007). Given the lack of durable response with standard chemotherapy in the relapsed ALL population, new agents are needed to increase the rate of CR and opportunity for transplantation, therefore improving the chance of long-term survival (Fielding et al., 2007; National Comprehensive Cancer Network, 2015). Treatment with bispecific T-cell engager (BiTE) antibodies is an appealing approach because they target a specific subtype of disease, use a distinct mechanism of action, and have a different side effect profile compared to traditional chemotherapy (Raponi et al., 2011). CD19 is an antigen expressed in almost all patients with precursor B-cell ALL, which makes this cell surface marker a valuable target.
for immunotherapy (Kantarjian, Thomas, Wayne, & O’Brien, 2012; Le Jeune & Thomas, 2014; Rapo et al., 2011). Blinatumomab (Blincyto®) is a BiTE antibody that binds to CD19 (found on B lymphoblasts) and CD3 (expressed on cytotoxic T cells) (Amgen, Inc., 2014). Concurrent binding of these cells results in T-cell–mediated lysis of both benign and malignant B cells. Blinatumomab engages the T cells to target and potentially eliminate precursor B-cell ALL blasts, with the goal of inducing a remission (Hoffman et al., 2005; Topp et al., 2015).

Blinatumomab received accelerated approval by the U.S. Food and Drug Administration (FDA) in December 2014 based on the results of a multicenter, single-arm, phase II study in 189 adult patients with high-risk relapsed or refractory Philadelphia (Ph) chromosome-negative precursor B-cell ALL (Amgen, Inc., 2014; Topp et al., 2015). Blinatumomab was administered as a 28-day continuous IV infusion, followed by a two-week treatment-free interval, for as many as five cycles. During cycle one, dosing was stepwise, starting with 9 mcg per day for one week and then 28 mcg per day until completion. CR or CR with partial hematologic recovery was achieved in 43% of patients within the first two cycles (Topp et al., 2015). Of the patients who responded, 82% achieved minimal residual disease negativity, and 40% received HSCT (Topp et al., 2015). Treatment-related adverse events typically occurred within the first cycle and included pyrexia, headache, febrile neutropenia, peripheral edema, nausea, hypokalemia, constipation, and anemia. Infusion reactions, which can occur within the first 48 hours of beginning therapy, include fever, hypotension, cytokine release syndrome (CRS), hypertension, myalgia, rash, face swelling, and tachypnea. Two black box warnings for blinatumomab are indicated. CRS occurred in 11% of patients, with 2% being considered severe and categorized as grade 3. CRS is a constellation of symptoms, which most commonly includes fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased total bilirubin. Cases of disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS (Amgen, Inc., 2014). In addition, neurologic toxicity developed in 52% of patients, with 11% categorized as grade 3 and 2% as grade 4 (Amgen, Inc., 2014). Grades 3 or higher toxicity included encephalopathy, convulsions, speech disorders, altered consciousness, confusion or disorientation, and disturbances in coordination or balance. The most common (greater than 10%) manifestations of neurological toxicity include headache, tremor, dizziness, and altered consciousness (Amgen, Inc., 2014).

Adverse event grading was based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (National Cancer Institute, 2014).

The study population was specifically selected for negative prognostic features, including early relapse, high disease burden, and multiple lines of prior salvage therapy (including HSCT), therefore making the response rates observed in this trial particularly noteworthy (Topp et al., 2015). The CR2 rates of 42%–45% with standard chemotherapy include a mixed population of patients with standard- and high-risk disease (Bassan & Hoelzer, 2011; Oriol et al., 2010). When looking at a high-risk population similar to that studied by Topp et al. (2015), the CR2 rates were 18%–25% (Gökbuget et al., 2012; O’Brien et al., 2008). In this context, the response seen with blinatumomab is significant and represents an effective treatment option for patients with relapsed or refractory Ph chromosome-negative precursor B-cell ALL (Topp et al., 2015).

Guidelines and Order Sets

Shortly after accelerated FDA approval, the first patient at the authors’ institution to be eligible for blinatumomab therapy was identified. Prior to initiating, it was quickly realized that a number of safety procedures and logistical processes needed to be in place, because blinatumomab is a new drug with many complexities regarding preparation, administration, monitoring, and coordinating the transition through phases of care. A strategy was developed to approach education, as well as address the necessary aspects of blinatumomab therapy.

Blinatumomab guidelines were created as a formal education document to be used by nursing, pharmacy, and medical staff. The guidelines incorporated a number of facets, including designated unit for administration, drug information (dosing, mechanism, dose adjustments, warnings/precautions, monitoring), pharmacy-specific information, nursing-specific information, and management of CRS and neurologic toxicities. Also included was a reference defining CRS per the CTCAE criteria (Lee et al., 2014).

Accompanying the guidelines were order sets to help direct safe and appropriate use of blinatumomab. The order sets encompassed the different phases of patients’ therapy, including admission orders, cycle 1 blinatumomab orders, subsequent blinatumomab cycle orders, and readmission in midcycle blinatumomab orders. The differentiation in these sets sought to distinguish the appropriate dose, rate of infusion, premedications, and preparation instructions needed for each potential admission during the treatment course. Indication for readmission may include fever, infectious complications, or drug-related toxicity requiring inpatient management and monitoring. These order sets also provided clarity and improved communication between the prescribers, pharmacy, and nursing staff regarding patients’ needs during each distinct phase of therapy.

The blinatumomab guidelines and order sets were approved by the appropriate institutional committees in a stepwise process. Feedback was encouraged from oncology and non-oncology clinicians, as well as safety administrators, throughout the process. These documents were then made available on the institution’s shared drive.

Education

To educate the multidisciplinary staff about blinatumomab, a medication guide was developed that highlighted...
key information for nursing and pharmacy staff. After education was complete, this guide served as an ongoing resource for nursing and pharmacy staff. Education included all shifts and was delivered by the leukemia nurse practitioner, oncology nurse specialist, nurse educator, and clinical oncology pharmacist. Nurses received the required training before caring for patients being treated with blinatumomab. Because blinatumomab is a drug with unique administration considerations and requires specific monitoring, arrangements were made to ensure that patients admitted for blinatumomab are assigned to a dedicated unit. Pharmacist education included details on drug preparation, dispensing, storage, and stability.

The blinatumomab medication guide continues to act as a resource for nurses in recognizing adverse events and determining the appropriate time to contact the provider. Nursing education included the importance of relaying clear and concise information to the prescriber. It is expected that the nurse can describe the patient’s symptoms and grade adverse events based on CTCAE guidelines. Guidance in these areas can help to ensure timely and appropriate management of blinatumomab-related toxicities.

### Nursing Considerations

Patients receiving blinatumomab require specific nursing assessment and monitoring focused around the potential side effects. Comprehensive laboratory testing prior to initiation of treatment is required. Patients receive premedication with dexamethasone 20 mg IV prior to the first infusion, prior to dose escalation, and prior to reinitiation of infusion if drug was held for four or more hours (Amgen, Inc., 2014). The institutional guidelines incorporate neurological checks and a patient’s signature log, both to be assessed by the nurse every shift. In addition, the nurses monitor closely for seizure activity. Any alterations in the neurological status, vitals, or laboratory results should be reported immediately to the nurse and dispensing pharmacist.

### CTCAE—Common Terminology Criteria for Adverse Events

- **Headache**
- **Tremor**
- **Dizziness**
- **Seizures**
- **Convulsions**
- **Speech disorder**
- **Altered consciousness**
- **Confusion or disorientation**
- **Disturbances in coordination or balance**

As experienced oncology nurses, the staff are accustomed to caring for central venous access devices (given the duration of infusion, many prescribers prefer central access for safety and patient convenience). With blinatumomab, some of the standard care and maintenance procedures of central venous access devices vary. To avoid administering an excessive dosage of blinatumomab, flushing the line is not recommended. Flushing inhibits the ability to assess for blood return during the infusion, which is standard practice with other chemotherapy and biotherapies (Amgen, Inc., 2014). The standard procedure for changing the caps of a central venous access device was modified based on the limitations of flushing the line. Communication of the patients’ response to treatment, the timing of medication administration, and cap changes must be clearly endorsed during shift report.

### Multidisciplinary Collaboration

Coordination with pharmacy staff is an essential component of care. The medication is stable at room temperature for 48 hours after reconstitution and mixing in a saline bag (Amgen, Inc., 2014). Communication between the nurse and dispensing pharmacist is particularly important to ensure proper handling and storage of the drug, as well as to provide notification of delays or changes in treatment to avoid drug wastage.

Collaboration with the case manager is recognized as another vital component of treatment. In the institution, the case manager is the individual who ensures insurance coverage for inpatient and outpatient therapy prior to initiation. In addition, they coordinate the logistics for transitioning from hospital to home with the patient and the home

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**FIGURE 1. Key Multidisciplinary Roles in Blinatumomab Coordination**

| Nurse |• Documentation of neurological function with patient’s daily signature log, in addition to standard neurological checks at each shift |• Management of blinatumomab inventory for adequate stock |
| |• Placement of “do not flush” stickers on IV infusion line to remind all staff that no flushing is permitted |• Physician or advanced practice nurse |
| |• Any alterations in the neurological status, vitals, or laboratory results reported immediately to the prescriber for further guidance |• Makes decisions regarding dose adjustments, interruption, or discontinuation of infusion based on clinical status, toxicities, laboratory data, and vital signs |
| |• Communication of the patient’s response to treatment, the timing of medication administration, and cap changes during shift report |• Communicates with other members of the clinical team regarding any modifications to the treatment plan |
| |• Relaying clear and concise information to the on-call prescriber based on CTCAE criteria |• Communication with pharmacy regarding any delays or changes to treatment schedule |
| |• Communication with pharmacy regarding any delays or changes to treatment schedule |• Pharmacist |
| |• Coordination with nursing that initiation of infusion is during daytime hours to assist with transition to home |• Coordination with nurse and physician or advanced practice nurse regarding details of discharge, including date, destination (i.e., home or subacute rehabilitation facility), and needs |
| |• Coordination with nursing regarding any delays or changes to treatment schedule |• Case manager |
| |• Drug stability information provided on admixture bag |• Obtains insurance approval for inpatient and outpatient therapy |
| |• “Refrigerate” sticker placed on bag to ensure proper storage if admixture is not immediately infused upon delivery |• Coordinates with nurse and physician or advanced practice nurse regarding details of discharge, including date, destination (i.e., home or subacute rehabilitation facility), and needs |
| | |• Home infusion company |
| |CTCAE—Common Terminology Criteria for Adverse Events |• Representative to provide patient and caregiver education on therapy and infusion pump prior to patient discharge |
| | |• Resource for patients once they are home if questions or toxicities arise |
infusion company. Information regarding expected discharge date and the patients’ needs are discussed among the case manager, nursing staff, and physician or advanced practice nurse on a daily basis during unit rounds.

Blinatumomab is administered as a continuous IV infusion for 28 days. Patients should remain hospitalized for the first nine days of cycle 1 and for the first two days of cycle 2 to ensure close patient monitoring and tolerability. Patients receive the majority of therapy in the outpatient setting via a home infusion company, outpatient cancer center, or outpatient infusion center. Involving the home infusion company early in the discharge process allows patients to absorb information during a period of time and to learn how to troubleshoot the infusion pump. Patients are often uncomfortable about going home with a continuous medication infusion and require ample support and education, particularly on how to manage the infusion pump and potential toxicities that may occur at home. The advanced practice nurse, oncology nurse specialist, and clinical oncology pharmacist serve as ongoing support among all disciplines to help facilitate successful administration throughout the treatment process. Each member of the multidisciplinary team plays an important role during different phases of the treatment (see Figure 1).

Conclusion

Blinatumomab has shown to be a promising therapy for patients with relapsed or refractory Ph chromosome-negative precursor B-cell ALL. A CR rate of 43% in a particularly high-risk patient population makes this drug an attractive treatment option (Topp et al., 2015). When instituting the therapy, processes must be in place to address the unique logistical and administration challenges (see Figure 2). Creating guidelines and order sets helps to standardize practice. Education is an essential component which should be delivered to all members of the healthcare team prior to initiation of blinatumomab and continued on an as-needed basis. Implementing therapies of this nature requires multiple phases of preparation and education across several disciplines to ensure safe and successful administration.

References


