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Dinutuximab: A Novel Immunotherapy in the Treatment of Pediatric Patients With High-Risk Neuroblastoma CE

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Abstract

Therapy combining dinutuximab with granulocyte macrophage colony stimulating factor, interleukin 2, and isotretinoin has significant side effects; however, these complications are generally predictable and can be managed proactively.

Keywords

immunotherapy, infusion management, patient safety

Background

Immune-mediated therapy used in the treatment of cancer has dramatically evolved over the past 15 years. Pediatric high-risk (HR) neuroblastoma (NBL) is one disease that has greatly benefitted from this immunologic evolution. NBL is the most common, noncentral nervous system solid tumor of childhood and occurs in about 650 North American children each year (Howlader et al., 2012). Over half of these children present with advanced disease and are classified "high-risk" (Brodeur, 2003). Historically, outcomes for HR NBL have been poor. Aggressive multimodal therapy treatment with chemotherapy, surgery, stem cell transplant, radiation, and biologic disease modifiers offered a 5-year event-free survival of only 30% (Matthay et al., 2009). A recent landmark study by Yu et al. (2010) demonstrated superiority with an anti-disialoganglioside (GD2) targeted chimeric monoclonal antibody (ch14.18) used in combination with the biologic disease modifier isotretinoin (ISOT), cytokines granulocyte macrophage colony stimulating factor (GM-CSF), and interleukin 2 (IL-2), compared to ISOT alone post standard HR therapy. This trial improved event-free survival to nearly 66% and is now considered standard of care in the maintenance phase of therapy for de novo pediatric HR NBL. Therapy consists of 5 courses of the anti-GD2 ch14.18, now known as dinutuximab, and ISOT alternating with IL-2 and GM-CSF and a 6th course of ISOT alone (see Figure 1). This combination therapy works synergistically with the immune response.

GD2 is a molecule on the surface of nearly all NBL cells, and its homogenous expression makes it an ideal target for immunotherapy (Schulz et al., 1984). Cytokines, such as GM-CSF and IL-2, are naturally present proteins in the body that stimulate the immune system. When administered exogenously in combination with dinutuximab, the immune-mediated cytotoxic effect on NBL cells is enhanced; dinutuximab identifies the cancer cells, and the cytokines aid in the assault. ISOT decreases proliferation and expression of NMYC, a gene mutation in NBL cells, and aids in the morphological differentiation of NBL cells (Thiele, Reynolds, & Israel, 1985).

Therapy combining dinutuximab with GM-CSF, IL-2, and ISOT has significant side effects; however, these complications are generally predictable and can be managed proactively. The administration of the GM-CSF and IL-2 cytokines can cause flu-like symptoms, such as fever, chills, myalgia, arthralgia, and can trigger capillary leak syndrome (CLS). CLS most often occurs when the IL-2 is given in combination with the dinutuximab (Schwartz, Stover, & Dutcher, 2002). In addition to the

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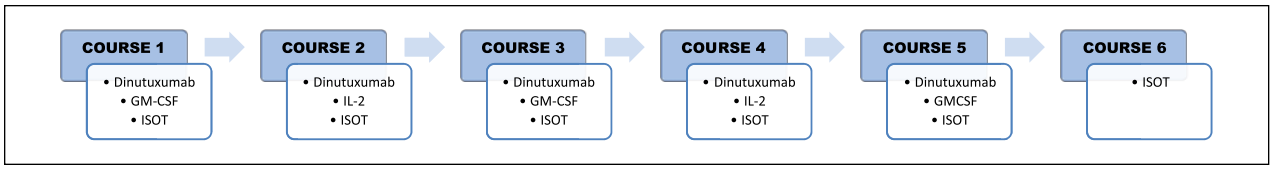

Figure 1. Immunotherapy treatment course.
Abbreviations: GM-CSF, granulocyte macrophage colony stimulating factor; ISOT, isotretinoin; IL-2, interleukin 2.

immune-mediated effects of this regimen, the specific binding of dinutuximab to nerve fibers, which also express GD2, causes significant pain during the infusion. Side effects of ISOT are primarily dermatologic, such as dry skin or cheilitis, that can be managed with topical emollients, they but can also include transient elevations in triglycerides (Taketomo, 2008, 2011).

Since the inception of Dr. Yu's trial in 2001, a wealth of previously uncaptured and underreported clinician experience regarding medication administration and side effect management has emerged. The goal of this article is to provide a framework for providers and nurses to create their own institution-specific standards for the management of care in patients receiving this immunotherapy.

Treatment Management Considerations

Pain

Dinutuximab targets the protein GD2 that is present on the NBL cell. Unfortunately, GD2 is also present on neurons and peripheral nerve fibers, thereby causing sensations of pain in the majority of patients receiving dinutuximab. Immunotherapy pain is generally immediate after start of the drug and usually subsides within a few hours after completion of dinutuximab; it primarily manifests as abdominal pain but may occur anywhere (Yu et al., 2010).

The use of opioids for the duration of the antibody therapy is essential. The opioid of choice is often morphine, but this decision is institution and patient specific. Few patients are opioid naive at this point in their therapy and therefore may require an alternate medication, high opioid doses, or rapid dose escalation to control the antibody-mediated pain associated with this therapy. Aggressive pain control is a priority, as the U.S. Food and Drug Administration (FDA) recommends permanent discontinuation of dinutuximab in patients with severe pain that is uncontrollable.

Providing patients with a bolus dose of narcotic prior to the dinutuximab infusion followed by immediate initiation of a continuous opioid is necessary. A demand dosing via a patient-controlled analgesia (PCA) pump is used to manage breakthrough pain. For patients who do not respond well to the initial drug chosen, an alternate opioid such as hydromorphone or fentanyl should be substituted or a lidocaine infusion may be added. Based on institutional practice, a specialist in pain medicine may be consulted.

Pain generally dissipates once the antibody infusion is completed, and the opioid is weaned approximately 1 hour after the daily immunotherapy is completed. A general recommendation is to decrease the continuous rate by 50% and then discontinue 2 to 3 hours later. Infrequently patients may experience pain hours after the antibody infusion is completed, and continued use of the narcotic after cessation of immunotherapy may be required. More routinely, the opioid is weaned off on completion of the dinutuximab infusion and is then restarted immediately prior to the next day's antibody infusion. If the dinutuximab infusion was prolonged or the opioid was weaned over a longer amount of time due to patient's pain level, the PCA infusions may be continued for the entire 4-day course of the dinutuximab and then tapered after the dinutuximab course is complete. Weaning opioids at the time of discharge is rarely unsuccessful; however, a patient may require an oral opioid taper as an outpatient if concerned that they may have withdrawal issues.

For subsequent courses, consider starting the patient at the highest dose of opioid required for adequate pain control during the prior course. Close monitoring is necessary with opioid initiation, as the severity of pain with subsequent courses has been shown to decrease (Ozkaynak et al., 2014; Yu et al. 2010). The goal of the opioid is adequate pain management without oversedation. Close monitoring and consideration of concurrent medications (most notably diphenhydramine) are essential strategies in maintaining adequate pain management without oversedating the patient.

Pruritus can often occur with both morphine and hydromorphone. Diphenhydramine, administered as an immunotherapy premedication, may ease opioid-induced itching. Hydroxyzine may be added for persistent pruritus. Alternately, based on institutional preference, a low-dose continuous naloxone infusion may be initiated along with the PCA to relieve persistent itching.

Apart from the characteristic pain managed with preemptive opioids, patients may develop neuropathic pain that does not respond well to the opioid alone. Gillin and Sorkin (1998) performed a study assessing gabapentin for pain control with an anti-GD2 antibody in rats and found that the medication was successful in blocking antibody-related neuropathic pain. Gabapentin may be added during immunotherapy as an adjunct for neuropathic pain and in subsequent courses can be started prior to initiation of dinutuximab (FDA, 2015). Anecdotally, adequate neuropathic pain control has been seen both when the gabapentin is started 2 days prior to the dinutuximab and discontinued at the completion of each course of immunotherapy and when the medication is continued daily until all the courses have been completed.

Fever

Following pain, fever is the next most common side effect, occurring in 39% of patients receiving immunotherapy (Yu et al., 2010). The etiology of fevers are influenced by a number of factors, including IL-2 induced release of pyrogenic factors (Siegel & Puri, 1991) and immune stimulation/cytokine release associated with antibody administration (Descotes, 2009). Because fever is an expected adverse effect during this treatment, administer acetaminophen as a premedication prior to the start of the antibody and continue every 4 to 6 hours until the infusion is complete. Patients may still become febrile despite continuous administration of acetaminophen, thus close monitoring of temperature is required. Persistent fevers may respond to the addition of ibuprofen or trilisate; however, institutional practices related to the use of alternate antipyretics vary and should be clarified prior to dinutuximab administration. While high fevers may be a cause of distress to family members and of discomfort to the patient, they are not an indication to stop antibody infusion.

Fevers may still indicate another complication, such as a bloodstream infection. For this reason, patients with a central line should always have blood cultures drawn from each lumen for surveillance every 24 hours of fever. Central line culturing should follow institutional practices that avoid bolus dosing such as withdrawing prior to flushing. Although this regimen of immunotherapy does not induce neutropenia, IL-2 therapy can induce defects in neutrophil function and place patients at higher risk for staphylococcal infections (Siegel & Puri, 1991). The overall incidence of sepsis while receiving this regimen is 18% (Yu et al., 2010).

The use of empiric antibiotics in febrile, nonneutropenic patients receiving dinutuximab varies per by institution. Given the risk of central line associated blood stream infections in any patient with a central line, some institutions have chosen to give empiric antibiotics in addition to obtaining blood cultures, while other institutions obtain surveillance cultures alone and initiate antibiotic therapy only in the presence of a positive culture. If a positive culture or any systemic infection develops, antibody therapy should discontinued for that course; minor infections such as an otitis media, typically do not alter therapy (FDA, 2015).

Hypersensitivity Reactions

Children receiving therapy with dinutuximab are at risk for hypersensitivity reactions, due to immune stimulation and cytokine release, with a greater incidence of reactions tending to occur during courses when both the antibody and IL-2 infusions are administered (Yu et al., 2010). Hydrocortisone and epinephrine should be kept ready at the bedside prior to initiation of therapy. Reactions range in severity and include rashes, and urticaria, to bronchospasm, wheezing, facial swelling, and anaphylactic shock (Parsons, Berndardt, & Strickland, 2013). Patients receiving immunotherapy should have diphenhydramine administered as a premedication, with continued dosing scheduled every 4 to 6 hours for prophylaxis. The addition of other antihistamine medications, such as hydroxyzine, cetirizine, or ranitidine, may also be beneficial in controlling hypersensitivity reactions. For patients whose symptoms do not improve with use of supportive medications, it may be necessary to pause or decrease the rate of antibody infusion based on the severity of the reaction. For mild to moderate adverse reactions, the infusion rate can be reduced by 50% with constant patient monitoring. If the reaction resolves, gradually increase the infusion rate back up to the maximum of 1.75 mg/m^2/hour (FDA, 2015).

Coughing may be an early sign of bronchospasm, and close monitoring is necessary as respiratory distress may immediately precede anaphylaxis. For persistent respiratory symptoms that do not improve with use of antihistamines and are bothersome but not compromising, treatment with nebulized albuterol may be beneficial. Racemic epinephrine should always be readily available as an emergency medication. Administration of oxygen, even in the absence of desaturations, may provide comfort and symptom relief.

Hypotension

Hypotension is a potential side effect of the antibody, reaching Grade 3 defined as requiring vasopressors for >24 hours, requiring intervention but without physiologic consequences, or Grade 4 with shock in 16% of study patients (Yu et al., 2010). It can, however, also occur in relation to opioids and other interventions of therapy. The risk of hypotension is greatest with opioid initiation due to the confounding factors of diphenhydramine premedication and the start of the

antibody infusion. Patients who consistently experience lower blood pressure with diphenhydramine may benefit from starting the premedication earlier and infusing it over a longer duration. A normal saline (NS) bolus of 10 mL/kg is infused over 1 hour prior to each dinutuximab dose to lessen the risk of hypotension by increasing intravascular volume. Blood pressure should be monitored frequently early in the infusion and then less closely as the infusion continues; often due to the continuous opioid infusion, children are placed on a cardiorespiratory monitor.

If hypotension occurs (systolic blood pressure calculated in children aged 1-10 years as 70 mm/Hg + [child's age in years × 2]; Chameides, Samson, Schexnayder, & Hazinski, 2011), interrupt the dinutuximab and IL-2 infusions and continue close monitoring. Hypotension often resolves by decreasing the rate of antibody infusion (Yu et al., 2010). If necessary, decrease the narcotic infusion and administer an NS bolus of 5 to 10 mL/kg. Caution when administering a NS bolus as it may exacerbate capillary leak. When the hypotension resolves, the dinutuximab infusion may be resumed at 50% of the previous rate. If after 2 hours the blood pressure remains within normal limits, the infusion may be increased as tolerated to the maximum 1.75 mg/m^2/hour, and the IL-2 may be resumed (FDA, 2015).

Extending the infusion duration from 10 to up to 20 hours has shown to decrease the incidence of hypotension. For patients who have had significant hypotension, subsequent infusions may benefit from starting at this prolonged duration.

If the hypotension does not promptly respond to hydration or stopping dinutuximab infusion, adrenergic vasopressors and transfer to intensive care unit may be necessary. It should be noted that dinutuximab and vasopressors cannot be given concurrently. Patients must be stable and off vasopressors before resuming dinutuximab infusion. Despite the immediate acuity of unresponsive hypotension, a prompt recovery is frequent and most often does not necessitate complete discontinuation of the dinutuximab (FDA, 2015).

Capillary Leak Syndrome

CLS can be life-threatening, leading to shock and multisystem organ failure. The pathogenesis of CLS is complex but is thought to occur when endothelial cells are damaged from the immune-mediated, cytotoxic response of dinutuximab, GM-CSF, and IL-2 (Baluna, 2007). This endothelial damage causes the vasculature to dilate and become more permeable, resulting in the leakage of intravascular fluids into the interstitial space of tissues and organs. Patients are at higher risk of developing CLS during courses when IL-2 and dinutuximab are given concurrently (Yu et al., 2010).

Early detection and intervention of this side effect are critical. Common signs and symptoms of CLS include peripheral/facial edema, increased weight, respiratory distress or crackles heard on lung exam, rising urine specific gravity, and decreased urine output with unbalanced intake and output measurements. Hemodynamic manifestations of CLS, including hypotension and tachycardia, require urgent intervention. Careful monitoring of patients is necessary as CLS may present gradually.

Assessment for CLS includes twice-daily weight checks and accurate measurement of intake and output balance every 4 hours, which may serve as early indicators of fluid retention. Daily monitoring of hemoglobin and serum albumin levels provides insight into a patient's vascular fluid status. Low levels of albumin and hemoglobin contribute to a decrease in serum oncotic pressure, resulting in an osmotic shift of fluid from the vasculature to the tissues. Maintaining hemoglobin ≥10 g/dL and serum albumin at the upper limit of normal achieves a higher oncotic pressure; therefore, the amount of fluid leaking from the capillaries is decreased, making the clinical symptoms of CLS less severe. As a result, many institutions transfuse packed red blood cells (PRBCs) for hemoglobin ≤10 g/dL and replace with 25% albumin when serum albumin nears the lower limit of normal for age. Administration of a diuretic, such as furosemide or metolazone, immediately after the administration of albumin or PRBCs can aid in removing excess extravascular fluid and prevent fluid overload. Minimizing IV fluids during dinutuximab therapy may also prevent excess fluid from leaking into the tissues and lungs; oral hydration is the preferred route of intake.

Despite efforts to maintain higher oncotic pressure, hemodynamic compromise due to CLS does occur. In this event, the antibody, IL-2, and GM-CSF should all be stopped and the patient assessed to determine the course of action. If fluid resuscitation is required for hypotension management, volume should start low at 5 to 10 mL/kg to minimize the risk for fluid overload. Administration of PRBC transfusions and albumin may correct the hypotension as well as assist in maintaining oncotic pressure and may be preferable to IV fluids.

If the symptoms of CLS resolve, resume the dinutuximab infusion at 50% of the rate, however, the IL-2 and GM-CSF should continue to be held. If the dinutuximab infusion is well tolerated, then the cytokines may be given at 50% of the dose with the next infusion day (FDA, 2015).

If the CLS is life-threatening, discontinue the dinutuximab for that course. Dinutuximab may or may not be resumed with the next course based on the sequence of patient events. If it is resumed, the dinutuximab should be given at 50% of the rate and if tolerated consider substituting the IL-2 with GM-CSF in the subsequent course. If

life-threatening CLS recurs, permanently discontinue the dinutuximab (FDA, 2015).

Additional Adverse Effects of Immunotherapy

In addition to the reactions described above, additional rare side effects can occur throughout the course of immunotherapy, including liver dysfunction (as evidenced by increases in ALT [alanine aminotransferase] and/or AST [aspartate aminotransferase]) and electrolyte disturbances. Hypokalemia can be especially prevalent in children requiring frequent administration of furosemide in association with CLS. Chemistry panels should be closely monitored, and if severe imbalances occur then electrolyte replacement and/or correction may be necessary. Nausea, vomiting, and diarrhea are also potential side effects, and supportive medications should be used as necessary for symptom relief.

Ocular changes such as mydriasis and accommodation issues (Kremens et al., 2002), as well as anisocoria and sluggish pupillary response, have occurred in a small population of patients. Patients should be monitored for photophobia, papillary reactivity, and visual changes. Interrupt dinutuximab patients experiencing dilated pupils with sluggish light reflex and resume at 50% dosing on resolution. Antibody therapy is rarely discontinued for ocular changes (Kremens et al., 2002).

Nursing Implications for Immunotherapy Administration

Pediatric oncology nurses play a significant role in the administration of the immunotherapy designed to treat NBL patients. Their knowledge and recognition of common infusion-related complications and toxicities as well as pertinent administration management enable patients to receive this complicated treatment regimen in a safe and timely manner.

Administration of immunotherapy with dinutuximab can be challenging; however, the benefits of this therapy justify its use despite the likelihood of infusion-related complications and toxicities. Mild persistent symptoms such as fever or rash are bothersome, yet due to the overall efficacy of this therapy in patients with NBL, emphasis should be placed on use of appropriate supportive measures necessary to persevere through the infusion. The potential adverse events may be frightening for patients and families; however, it is important to note that most resolve soon after the antibody infusion has ended (Yu et al., 2010). Clear communication with patients on the expected toxicities as well as proactive and comprehensive supportive care are integral components for nurses to ensure successful completion of antibody infusions.

Administration Strategies

Through collaborative efforts of bedside nurses, nurse practitioners, nurse educators, and the compilation of educational materials from various health care centers the following administrative principles are recommended for patients receiving dinutuximab, GM-CSF, IL-2, and ISOT:

- *Day of admission*: Early admission times ensure all supportive services are present for a timely infusion start and for maximum availability in the event of side effects. Some institutions admit patients the day prior to day 1 of therapy for blood products, to confirm labs are within parameters and assure an early start to the antibody the following day.
- *Patient/nurse ratio*: Most institutions establish a 2 to 1 patient to nurse ratio on a hematology/oncology inpatient unit. Intensive care monitoring may be necessary for severe toxicity complications.
- *Dinutuximab infusion rate*: Rate of dinutuximab is initially set to infuse within 10 hours; decrease rate of administration as necessary based on the adverse effects experienced. Infusion-related complications may be eased by reducing the infusion rate; however, the maximum infusion time is 20 hours and any remaining dinutuximab after 20 hours must be discarded.
- *Vascular access issues and recommendations*: Double lumen central line access is preferred due to the need to administer numerous concomitant medications. For children with single lumen access, placement of a peripheral access line is necessary during courses with IL-2 administration. Nurses should review vascular access and pump configuration for immunotherapy and supportive care medications prior to beginning the course. Dinutuximab is not compatible with any other drug, and IL-2 is compatible only with morphine and D5W (5% dextrose in water).
- *Clinical monitoring*: Weigh patient twice a day and maintain close monitoring of vital signs for signs of hypotension, fever, tachypnea, and tachycardia. Rashes and edema are also assessment specifics that should be monitored closely.
- *Laboratory blood draws*: Do not interrupt the infusion line of dinutuximab to draw labs due to increased risk of giving "mini bolus" of medication when the line is flushed for the labs.

Dinutuximab Case Study

The following case study illustrates the application of these principles and the management of common treatment-related side effects (see Figure 2):

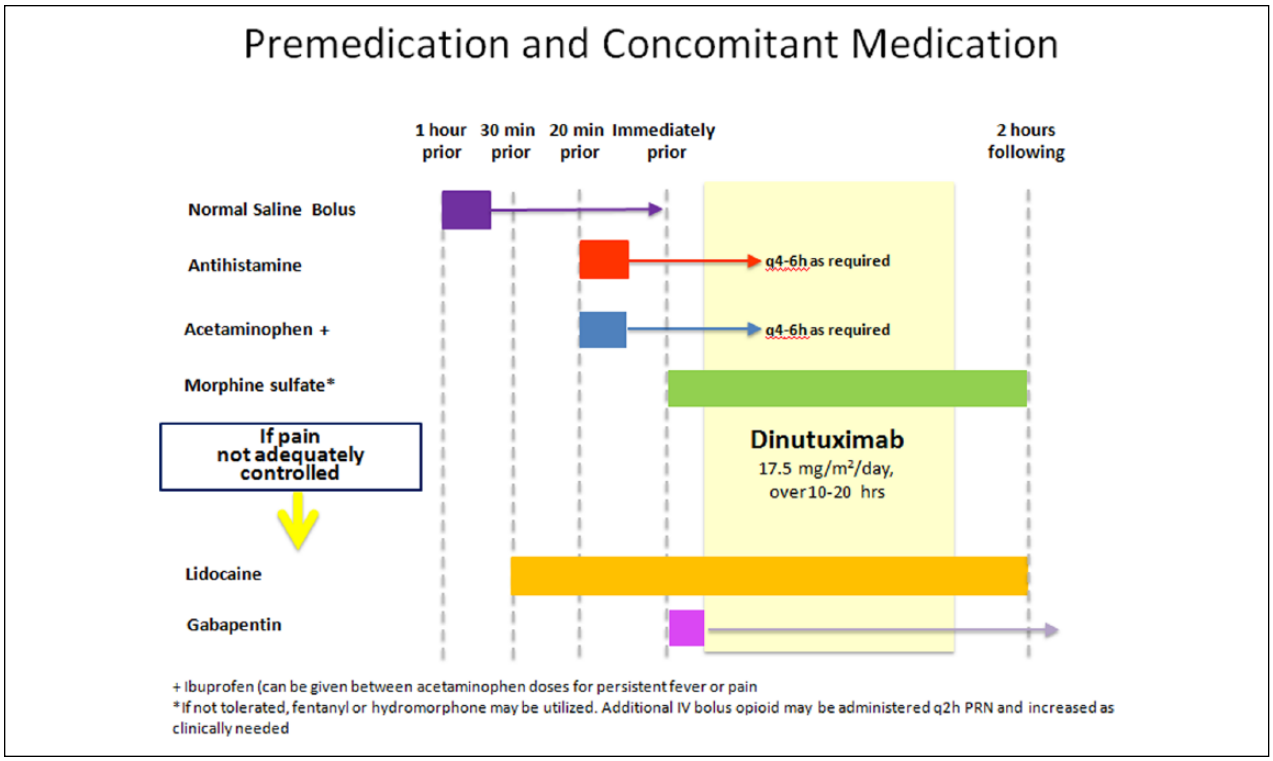

Figure 2. Dinutuximab administration: Supportive care measures at a glance.

A 3-year-old boy with Stage 4, HR NBL presented for immunotherapy course 2 with dinutuximab and IL-2. Premedications and fluids were administered prior to initiation of dinutuximab. Morphine was bolused at 0.05 mg/kg, and a continuous rate of 0.03 mg/kg/hr, and demand dose of 0.02 mg/kg/dose every 10 minutes was initiated.

Four hours into the dinutuximab infusion, complaints of severe abdominal pain rated 8/10 on Wong–Baker FACES® Pain Rating Scale developed. The PCA bolus was pushed 8 times, compared to 2 times the previous hour. A rescue dose of 0.05 mg/kg of morphine was given, and the patient's continuous and bolus dose PCA were increased by 50%. There were no symptoms of oversedation despite increased opioid doses and concurrent diphenhydramine. Pain decreased and remained 0/2 the remainder of the day.

On day 2, the opioid was initiated at previous day's escalated dosing. Despite diphenhydramine, premedication, pruritic hives developed on the patient's bilateral cheeks and upper trunk 5 hours into the infusion. His respiratory effort remained normal without cough so no infusion adjustment was made. Diphenhydramine, cetirizine 5 mg, and ranitidine 1 mg/kg/doses were given and scheduled henceforth. He remained stable, and his symptoms resolved within 15 minutes.

Eight hours into the infusion a fever of 39.9°C developed despite scheduled acetaminophen. He was mildly tachycardic without signs of hemodynamic instability. Blood cultures were drawn from both central line lumens and and ibuprofen 10 mg/kg was administered.

On the morning of day 3, his weight had increased 1 kg, and he had mild periorbital edema with clear lungs and stable vital signs. The infusion was started and by Hour 8 his urine output decreased to less than 1 mL/kg/hr. He was tachycardic with low normal blood pressures (77/43 mm Hg) for the duration of the dinutuximab. At the conclusion of the infusion, his capillary refill had increased to 4 seconds, and his weight had increased another 0.5 kg. A 5 mL/kg NS bolus with 25% albumin (1 g/kg) was given with improved urine output and blood pressure to 85/48 mm Hg. The edema persisted, but his lung exam remained clear.

On the morning of day 4, he remained mildly edematous with stable vital signs. His hemoglobin level was 9.1 g/dL so a PRBC transfusion was given, followed by a dose of furosemide (0.5 mg/kg). The dinutuximab infusion began as scheduled. The mild edema persisted, and at the completion of the day 4 infusion, the PCA was discontinued and patient was discharged home.

Patient and Family Education

Education is vital for families and patients receiving this therapy. Nurses and nurse practitioners should ensure

families are prepared for treatment by discussing the key points below:

- Educate patient and family prior to each course of therapy, the immunotherapy agents that will be given in that course, how they are administered along with their common side effects, and the supportive care drugs that will be used to treat the particular side effect.
- Educate parents on the subcutaneous administration of GM-CSF.
- Design a monthly calendar listing scheduled admissions and immunotherapy medications given at home (ie, GM-CSF, ISOT, and possibly low-dose IL-2).
- Use other educational material to assist in the understanding of immunotherapy administration and management of toxicities (United Therapeutics Corp, 2015, https://www.unituxin.com/education-resources/parent-caregiver-resources)

Future Directions

Immunotherapy with dinutuximab is a challenging therapy regimen for pediatric oncology nurses to administer to HR NBL patients. Strong collaboration with nurse practitioners, nurse educators, and bedside nurses with experience in delivering this type of novel therapy has resulted in the development of patient/family education and adverse reaction management materials for the commercial use of dinutuximab. Education symposiums offered at professional nursing conferences such as the Association of Pediatric Hematology/Oncology Nurses and access to education webinars will enable pediatric oncology nurses to have a more comprehensive understanding of this treatment. With this collective knowledge and approaches to patient management, patients will be able to receive this complicated treatment regimen in a safe and timely manner especially at institutions that are providing this therapy regimen for the first time.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Joy Bartholomew, Sharon Bergeron, Danelle Nelson, Lindsey Quirk and Jennifer Saggio are on the speakers bureau for United Therapeutics.

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