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THERAPY IN PRACTICE

Multidisciplinary Clinical Care in the Management of Patients Receiving Anti-GD2 Immunotherapy for High-Risk Neuroblastoma

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Abstract

The addition of anti-disialoganglioside-2 (GD2) monoclonal antibodies (mAbs) such as dinutuximab and naxitamab to standard therapies for high-risk (HR) neuroblastoma has significantly improved outcomes for children with this devastating disease. The care for these young patients receiving treatment for HR neuroblastoma is complex, with need for the involvement of a multidisciplinary team. Clinical implementation of anti-GD2 mAb treatment requires the same harmonized team approach. The authors share the development process of this coordinated team method and practical recommendations for administration of anti-GD2 mAbs and adverse event (AE) management. Successful collaboration between nurses and other team members ensures optimal treatment and comfort of patients and their families. The primary focus of this approach is to mitigate and manage AEs associated with anti-GD2 mAb treatments, such as pain, hypotension, allergic reactions, and hypertension, and to ensure safe and effective use of anti-GD2 mAbs. The two treatments approved for use in patients with neuroblastoma, dinutuximab for patients with HR disease following a partial response or better to frontline multimodal therapy and naxitamab for refractory or relapsed HR disease in the bone or bone marrow, were studied in different administration settings and follow different regimens and infusion schedules. Therefore, AE management requirements are specific to each treatment. The awareness of these differences and implementation of appropriate AE management strategies in clinical practice are important to ensure the best possible outcomes for patients with HR neuroblastoma.

Key Points

Caring for patients receiving treatment with dinutuximab or naxitamab requires a nurse-centered multidisciplinary team.

Practical guidance is given for managing adverse events including guidance that is common to both dinutuximab and naxitamab and that which is specific to each.

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1 Introduction

Approximately 50% of patients with neuroblastoma present with high-risk (HR) disease [1, 2]. Patients treated with traditional therapy regimens experience a recurrence rate of > 50% due to residual disease resulting in poor clinical outcomes [3, 4].

Two disialoganglioside-2 (GD2)-targeted monoclonal antibodies (mAbs), dinutuximab and naxitamab, have been proven efficacious in treating neuroblastoma by targeting GD2, which is highly expressed on the surface of neuroblastoma cells and has limited expression on normal tissue cells, improving outcomes in these patients versus non-mAb treatments alone [3–7]. Both anti-GD2 mAbs are approved by the US Food and Drug Administration (FDA); both are administered as intravenous (i.v.) infusions. The chimeric mAb dinutuximab (ch14.18), combined with granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), is indicated for the treatment of pediatric patients with HR neuroblastoma who achieve a partial response (PR) or better to prior first-line multiagent, multimodality therapy. The approval of dinutuximab in the USA in 2017 was based on results

of the Children's Oncology Group (COG) ANBL0032 phase 3 trial (NCT00026312) [3]. Although included in the dinutuximab label, IL-2 use has declined following a publication indicating no improvement in clinical efficacy [8]. The humanized mAb naxitamab (hu3F8) is indicated in combination with GM-CSF for the treatment of pediatric patients aged > 1 year and adult patients with relapsed or refractory HR neuroblastoma limited to the bone or bone marrow who have demonstrated a PR, minor response, or stable disease to prior therapy [9]. This indication received accelerated approval from the FDA in 2020 based on overall response rate and duration of response from the phase 2 Trial 201 (NCT03363373) [9] and the phase 1/2 Trial 12-230 (NCT01757626) [10]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. In Trial 201, 95% of naxitamab infusions were administered in the outpatient setting [11].

Adverse events (AEs), including infusion-related reactions, neurotoxicity, pain, hypotension, allergic reactions, and hypertension, are seen with all anti-GD2 mAbs; however, infusion duration and administration setting (inpatient vs. outpatient) differ between dinutuximab and naxitamab—therefore, the approach to AE management should be refined for each. This review aims to describe how AEs experienced by patients with HR neuroblastoma during dinutuximab and naxitamab infusions are managed from a multidisciplinary perspective. It provides practical guidance, based on the authors' experiences, for the prevention and management of AEs before, during, and after anti-GD2 mAb infusions. Specific recommendations for each mAb will be provided as appropriate, as well as guidance to optimize the multidisciplinary team approach to AE management.

2 Administration of Anti-GD2 Monoclonal Antibodies

The administration regimens for dinutuximab and naxitamab are shown in Table 1. Dinutuximab treatment is repeated over four consecutive days per cycle, up to a recommended five cycles [12]. Naxitamab treatment cycles are repeated

Table 1 Summary of administration regimens for dinutuximab and naxitamab in patients with refractory or relapsed high-risk neuroblastoma [9, 12]

Administration regimen characteristic	Dinutuximab	Naxitamab
Clinical trial setting	Inpatient	Outpatient
Dosing	17.5 mg/m^2/day as i.v. infusion	3 mg/kg/day as i.v. infusion (9 mg/kg/cycle)
Administration schedule	Infusion on 4 consecutive days of five cycles:	Infusion on days 1, 3, and 5 of each 28-day treatment cycle repeated until partial or complete response, followed by five additional cycles every 4 weeks
	Cycles 1, 3, and 5 are 24 days in duration, with dinutuximab administration on days 4–7	Subsequent cycles may be repeated every 8 weeks
	Cycles 2 and 4 are 32 days in duration, with dinutuximab administration on days 8–11	
	Some hospitals use 28-day cycles only, where dinutuximab is administered on days 4–7 of cycles 1–5	
Infusion rate	Infusion over 10–20 h	First infusion of cycle 1 day 1 given over a minimum of 1 h
	Infusion started at 5 cc/h (0.875 mg/m^2/h) for 30 minutes, followed by gradual increase to a maximum rate of 10 cc/h (1.75 mg/m^2/h) as tolerated	Infusion time typically ranges from 30–60 min depending on patient tolerability
	If the infusion is not tolerated at 10 cc/h, at any point, the rate can be decreased to 5 cc/h	If infusion is tolerated, subsequent infusions are given over a minimum of 30 min
Concomitant medication	Cycles 1–5:	All cycles:
	GM-CSF s.c. (or i.v. over 2 hours): 250 μg/m^2/day on days 1–14	GM-CSF s.c.: 250 μg/m^2/day on Days −4 to 0
	RA p.o. on days 11–24:	GM-CSF s.c.: 500 μg/m^2/day on days 1–5 (≥ 1 h before naxitamab administration on days 1, 3, and 5)
	Patients weighing ≤ 12 kg: 2.67 mg/kg b.i.d.	
	Patients weighing > 12 kg: 80 mg/m^2 b.i.d.	

b.i.d. twice daily, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *i.v.* intravenous, *p.o.* oral, *RA* 13-cis-retinoic acid, *s.c.* subcutaneous

every 4 weeks until complete response or PR, followed by five additional cycles every 4 weeks. Subsequent cycles may be repeated every 8 weeks until disease progression or unacceptable toxicity [9].

3 Managing Patients During Anti-GD2 Therapy

3.1 Multidisciplinary Team and Nursing Considerations

A multidisciplinary team helps improve patient and caregiver experience during treatment [13–15]. Key team members are shown in Fig. 1. Nurses play a crucial role within this team, with responsibilities including education of staff, patients, and caregivers; ensuring appropriate equipment and therapies are available at the bedside to mitigate AEs; assessment and management of AEs during and post-infusion; and coordination of tasks with other team members.

Assigned nurses should be Pediatric Advanced Life Support certified (or local equivalent) and have adequate experience in administering oncology treatments and immunotherapies, in addition to managing infusion-related reactions (IRRs).

For dinutuximab, one nurse per patient is typically required during the initial infusion, whereas two nurses are recommended for naxitamab, as the onset of acute pain and hypotension is faster and, therefore, immediate intervention should be available if needed. Additional team members ensure adequate support during assessment, monitoring, treatment, and documentation of the infusion and AEs (Fig. 1).

3.2 Preparation of Patients and Caregivers

Knowledgeable anti-GD2 therapy healthcare providers, such as a (pediatric) oncologist, advanced practice provider, or nurse specialist, should educate caregivers and patients on all aspects of the infusion. A child life specialist can assist with explaining the treatment and AEs to patients and prepare distraction objects for patients to have during infusions (i.e., games, computer tablet to watch favorite movie/TV show, headphones/earbuds for music, etc.). It is important to note that the experience can be especially intense during the first treatment cycle, particularly on the first day of the cycle. Connecting the family with others who have experienced anti-GD2 treatment may also be helpful.

Patients may be advised to arrive with an empty stomach for naxitamab infusions as a prevention for nausea and vomiting. The same recommendation is not routine for dinutuximab

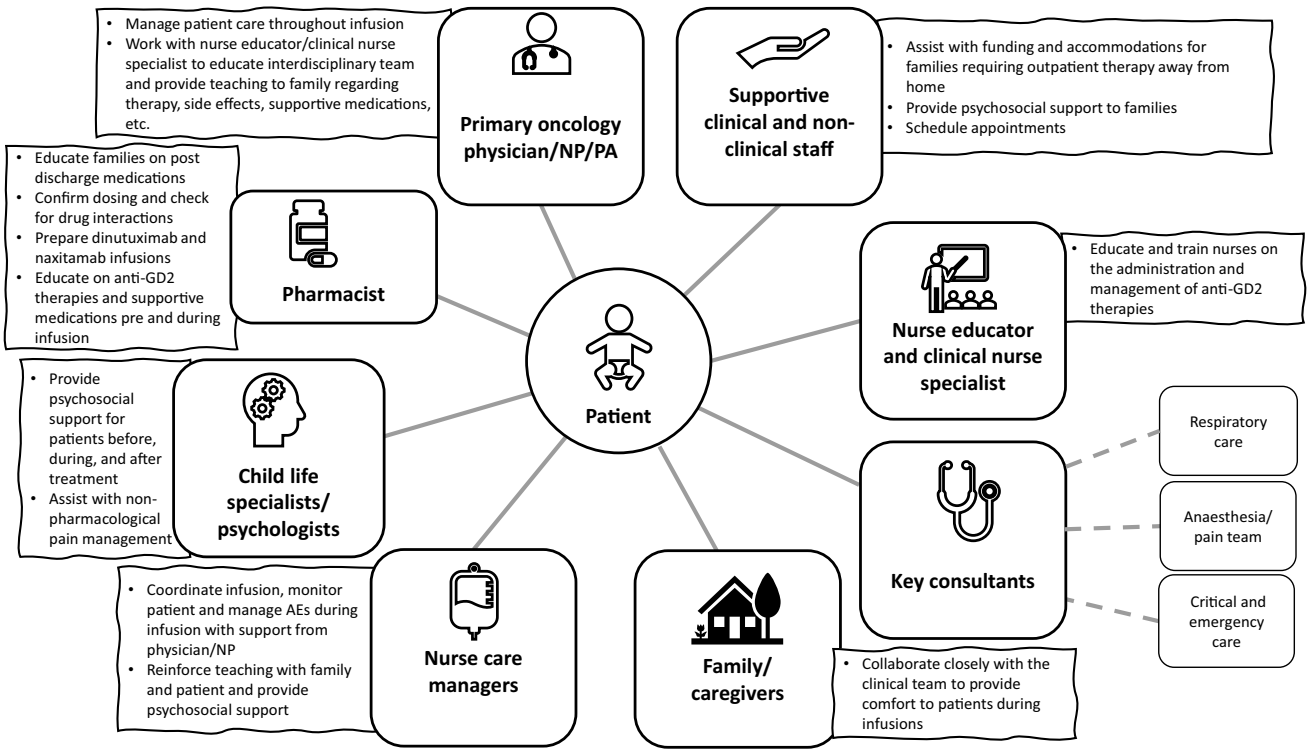

Fig. 1 The role of key multidisciplinary team members in patient care during anti-GD2 infusions. *AE* adverse event, *GD2* disialoganglioside-2, *NP* nurse practitioner, *PA* physician assistant

infusions due to fewer reports of nausea and vomiting with prolonged infusions, and it would not be ideal for a patient to fast before and for the duration of a 10- to 20-h infusion.

3.3 Infusion Practical Preparation

Organized preparation, including infusion discussions within the multidisciplinary team, is critical to ensuring optimal patient care and safety throughout infusions. It is strongly advised that all necessary information be readily available, such as safety information, an individualized list of premedications, room set-up, emergency medication, equipment checklists, guidelines for infusion administration, and monitoring and management of potential AEs.

All pertinent team members must be informed of patient admission/arrival time and planned infusion start times. Additionally, a review of all patient therapy and supportive care orders, as well as physical and laboratory results, must be completed before the infusion. Sufficient time must be allowed for infusion nurses to prepare medications, set up monitoring and emergency equipment, and administer premedication, including i.v. saline. Nurses should also use this time to ensure well-functioning central venous/i.v. access for the infusion, and if required, arrange an additional peripheral venous access for administration of i.v. medications during the infusion. A large room with space for equipment, supplies, and clear access to the patient is optimal. The bed should have sufficient space for parents to be near the child for comfort and should allow for use of the Trendelenburg position.

The following items should be available in the infusion room: respiratory support (non-rebreather mask, simple face mask, nebulizer kit, blow-by oxygen, suction, and bag-valve-mask resuscitator), rapid i.v. fluid bolus line with normal saline (required for emergency situations, should be primed and connected to patients during infusion), manual blood pressure (BP) and/or Doppler measurement (if continuous BP monitoring equipment is not available; Dopplers can also be used if unable to obtain BP reading with a manual cuff or if BP is difficult to hear at baseline), continuous oxygen monitors (pulse oximeter or continuous mobile monitor), electrocardiogram monitors, positional supports (e.g., pillows, blankets), emesis basins and face cloths, distraction objects, and warm/cold packs for comfort and pain relief. A crash cart should be readily accessible for both infusions. It is critical to have emergency and supportive medications pre-drawn before starting naxitamab infusions as AEs may occur more acutely with the shorter infusion duration.

Furthermore, caregivers must be prepared for anaphylactic reactions, which can occur with anti-GD2 mAbs and are potentially life threatening. As per institutional guidelines, treatment for anaphylaxis (such as i.v./intramuscular (i.m.) epinephrine or i.v. bolus hydrocortisone) must be available at the patient's bedside. Racepinephrine or an equivalent inhalant must be available pro re nata (as needed; PRN) for stridor, and levalbuterol or comparable selective β2-adrenergic receptor agonist (bronchodilator) for bronchospasm/lower respiratory issues.

3.4 Patient Care During and After Infusions

Nurses play a key role in patient monitoring during and after administration of anti-GD2 mAbs (Fig. 2). Continuous monitoring of vital signs and assessment of pain, respiratory status, mental status, and perfusion are important during infusions. For dinutuximab, vital signs should be monitored before the infusion, every 15 min during the first 1.5 h of the infusion, then hourly until completion of the infusion [12]. For naxitamab, vital signs should be monitored as clinically indicated, but at least before administering premedication, before PRN opioids/analgesia, before the infusion, at start of the flush, at the completion of flush (i.e., the end of the infusion), and at least every hour while recovering, for ≥ 2 h, until discharge criteria are met [9].

As dinutuximab is no longer routinely used with IL-2, the incidence of capillary leak syndrome (CLS) has decreased [8, 16]. However, it is recommended to monitor patients' hemoglobin and serum albumin levels daily during dinutuximab infusions and ensure that hemoglobin levels are ≥ 10 g/dL and serum albumin levels are ≥ 3 g/dL before infusion. In some institutions, dinutuximab infusions are extended overnight (up to 20 h) if hemoglobin levels are < 10 g/dL. Additionally, some institutions recommend transfusion of packed red blood cells or 25% albumin to meet these parameters, followed by a diuretic to remove excess fluids [17]. Patients' weight may be monitored twice daily during dinutuximab infusion to ensure they are not overloaded with fluid or experiencing CLS. If the patient's weight increases by 10% from the initial admission weight during dinutuximab infusion, albumin and/or furosemide can be administered.

Although the patient is usually stable shortly after the infusions, continued monitoring is essential for ≥ 4 h following dinutuximab and 2 h following naxitamab infusions. Patients treated with dinutuximab are usually discharged the day after the last infusion in the cycle, if clinically stable. For naxitamab, patients are discharged on the day of infusion after the post-infusion monitoring period, provided AEs have been resolved and vital signs are acceptable. Before discharge, the interdisciplinary team must provide instructions to caregivers regarding timing and administration of supportive home medications, how to monitor for potential AEs, and when to return to hospital and/or request assistance.

Debriefing as a team and with caregivers is useful for reviewing the patients' infusion experience and to further optimize AE management strategies. Support services,

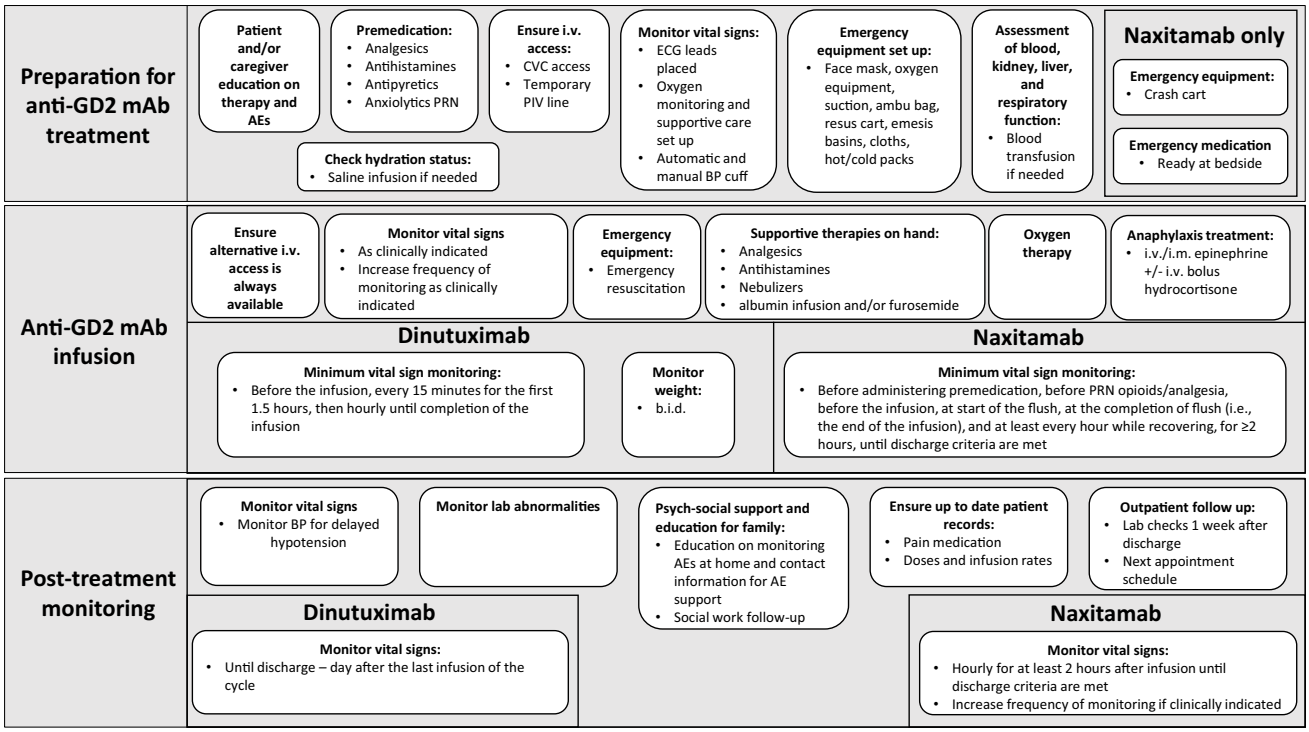

Fig. 2 The role of nurses in the process of care before, during, and after anti-GD2 mAb infusion. *AE* adverse event, *b.i.d.* twice daily, *BP* blood pressure, *CVC* central venous catheter, *ECG* electrocardiogram, *GD2* disialoganglioside-2, *ECG* electrocardiogram, *i.m.* intramuscular, *i.v.* intravenous, *mAb* monoclonal antibody, *PIV* peripheral intravenous, *PRN* pro re nata [as needed]

including social work, psychology, or peer support may be recommended to caregivers and team members who experience distress during the infusion.

4 Management of Common Adverse Events During and Following Anti-GD2 Therapy

A different approach to AE management is needed for dinutuximab and naxitamab due to the differences in drug administration, dosing, and setting, which influence the onset, duration, and severity of AEs. The most common AEs experienced during anti-GD2 treatment include pain, hypotension, IRRs, and fever (Table 2). The interdisciplinary team should monitor for AEs and intervene as necessary.

4.1 Pain

Acute pain is one of the most common AEs associated with anti-GD2 infusions [19, 20]. Pain usually starts within minutes of the infusion and gradually decreases after the infusion. Locations often affected are the abdomen, neck, back, sternum, and extremities. General anti-GD2 pain management recommendations include premedication, breakthrough pain medication, post-infusion medication, and nonpharmacologic pain management strategies.

Pediatric-appropriate pain assessments are an essential part of pain management for dinutuximab and naxitamab infusions. Nonverbal pain observations such as Face, Legs, Activity, Cry, Consolability (FLACC), or the faces pain scales can be used for neonates and pre-toddlers, and the numerical visual analog scale or verbal scale (both 1–10) can be used for older children.

Premedication with gabapentin is recommended for both dinutuximab and naxitamab treatment. With dinutuximab, gabapentin is recommended for patients for whom opioids provided inadequate pain relief [12], with schedules starting either 1 week before the infusion or on the day of the infusion [17]. For naxitamab, all patients receive a 12-day course of gabapentin, beginning 5 days before the first infusion and continuing until day 7 [9]. Dosing can be titrated based on the individual patient's needs (Table 3).

For dinutuximab, nurse-controlled analgesia (NCA) or patient-controlled analgesia (PCA) infusion of opioids (i.e., morphine, hydromorphone, or fentanyl) starts 1 h before the infusion. An i.v. loading-dose of pain medication (e.g., morphine sulfate) is given immediately before the infusion, and the NCA/PCA is continued for $\leq$ 2 h after the infusion, or as per patient history [12, 21]. For intense pain, the PCA is sometimes continued throughout the infusion cycle until 2 h after the last dinutuximab infusion. NCA/PCA dosage settings should always begin with a bolus dose

Table 2 Overview of key adverse events (AEs) observed with dinutuximab and naxitamab [9, 12, 18]

AE category	Dinutuximab	Naxitamab
AEs observed in ≥ 25% of patients in pivotal studies	General: pain, pyrexia, IRRs	General: pain, IRRs, fatigue, pyrexia, injection site reaction, anxiety, irritability
	Cardiovascular: hypotension, CLS	Cardiovascular: hypotension, tachycardia, hypertension
	Pulmonary: cough	Pulmonary: cough
	Gastrointestinal: increased ALT, increased AST, nausea, vomiting, diarrhea	Gastrointestinal: nausea, vomiting, diarrhea, decreased appetite
	Dermatologic: urticaria	Dermatologic: erythema multiforme, urticaria, edema
	Hematologic: thrombocytopenia, lymphopenia, anemia, neutropenia	Neurologic: peripheral neuropathy, headache
	Electrolytes: hypokalemia, hypoalbuminemia, hypocalcemia	
Black box warning	Serious infusion reactions and neurotoxicity	Serious infusion reactions and neurotoxicity
	IRRs (including facial and upper airway edema, dyspnea, bronchospasm, stridor, urticaria, and hypotension) and anaphylaxis	IRRs (including cardiac arrest, anaphylaxis, hypotension, bronchospasm, and stridor)
	Neuropathy (severe neuropathic pain, transverse myelitis, peripheral sensory neuropathy; motor neuropathy in adults)	Neurotoxicity (severe neuropathic pain, transverse myelitis, and RPLS)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CLS* capillary leak syndrome, *IRR* infusion-related reaction, *RPLS* reversible posterior leukoencephalopathy syndrome

and a low background infusion, titrating upwards until pain is controlled or the maximum recommended dose has been reached. It may be beneficial to choose NCA over PCA for patient safety during the infusion, as opioids can exacerbate hypotension, and overdosing can lead to respiratory depression. In subsequent cycles, the opioid infusion can begin at the dose that provided effective pain control during the previous cycle and be adjusted as required. Pain management specialists should always be consulted on NCA/PCA dosage settings and if any adjustments are needed. If pain during dinutuximab infusion is inadequately managed with opioids, lidocaine or gabapentin can be administered in conjunction with i.v. opioids [12, 22].

Oral opioids are preferred over i.v. opioids as premedication before naxitamab infusion, as they are associated with a reduced risk of AEs such as hypotension, respiratory suppression, and decreased responsiveness, with i.v. opioids reserved for breakthrough pain during naxitamab infusion [10, 23, 24]. An oral opioid such as hydromorphone or oxycodone can be administered before the infusion (Table 3). With the potential for acute onset of pain and increased risk of hypotension, continuous i.v. infusion is not used for administration of opioids with naxitamab. Breakthrough pain can be managed using low-dose (i.e., quarter-dose) i.v. opioids (Table 3). As the pain with naxitamab is acute and generally dissipates within 0.5–2 h of infusion completion, rapid-acting opioids with a short half-life are recommended. If pain during dinutuximab or naxitamab infusion is inadequately controlled, the premedication dose of opioids and/or gabapentin and the i.v. dose of opioids can be carefully titrated up.

Ketamine may also be used to manage pain; however, its use is dependent on institutional guidelines and requires consultation with pain management specialists to avoid deep sedation and anesthetic or dissociative side effects. The dose is based on age, weight, previous experience with anti-GD2 therapy, and, where available, history of AEs during prior ketamine experience (e.g., altered neurological status). Ketamine can be administered orally or as a constant i.v. infusion or bolus. Bertolizio et al. [21] reported effective pain control during dinutuximab infusion using continuous ketamine infusion, whereas Mora and colleagues [25] reported that a bolus allowed completion of treatment with naxitamab and reduced post-cycle recovery time [25]. The use of low-dose continuous infusion of ketamine for pain control during naxitamab infusions is under investigation [25].

Other pharmacologic pain management options include acetaminophen, which can be given to patients as premedication 1 h before starting the anti-GD2 infusion. For dinutuximab infusions, acetaminophen can be given every 4–6 h during infusion or repeated every 4 h PRN. If platelet levels are adequate, ibuprofen can be given post-infusion for pain and fever that is unresponsive to acetaminophen. Temperature should be checked before administering acetaminophen or ibuprophen and if febrile, the patient should be assessed for possible infection.

Nonpharmacologic strategies for managing pain may be valuable for patients receiving naxitamab or dinutuximab treatment. Patient/family preferences and child life

Table 3 Premedications and supportive therapies recommended for the management of adverse events (AEs) during administration of anti-GD2 therapy [9, 12]

AE category	Dinutuximab	Naxitamab
Pre-infusion[a]		
Pain	Gabapentin: initiate p.o. 1 week before expected start date of dinutuximab and increase to full dose by start of dinutuximab	Gabapentin: give as a 12-day course (day −4 through day 7); initiate p.o. 5 days before the first infusion and titrate during first 3 days (day −4 to day −2) (5–10 mg/kg with a max. dose of 600 mg/dose)
	Day 1: 5–10 mg/kg/dose (max. 300 mg/dose) at bedtime	Day −4: 5–10 mg/kg/dose q.d.
	Day 2: 5–10 mg/kg/dose (max. 300 mg/dose) b.i.d.	Day −3: 5–10 mg/kg/dose b.i.d.
	Day 3–7: 5–10 mg/kg/dose (max. 300 mg/dose) t.i.d.; should reach this dose by the time of admission for day 1 of the dinutuximab cycle	Day −2 to7: 5–10 mg/kg/dose t.i.d.
	Continue throughout dinutuximab treatment (may be given on days 4–7 of each cycle, in parallel with the initial pre-infusion dose of morphine or 2 days in advance)	Ketorolac 0.5 mg dose i.v. (max. daily dose 90 mg) if platelet count > 50×10^3/μL or ibuprofen 10 mg/kg/dose (max. 400 mg) p.o. q6 h PRN if platelet count > 50×10^3/μL and no history of GI bleeding
	Ketorolac (provided platelets > 50×10^3/μL): 0.5 mg/dose i.v. (max. daily dose of 90 mg)	Oral opioid (e.g. oxycodone 45–60 min pre-infusion, 0.1–0.2 mg/kg with a max. dose of 5 mg) or i.v. (e.g. hydromorphone (if p.o. not feasible) 15 min pre-infusion, 0.00375–0.015 mg/kg (over 2–10 min) or morphine sulfate 0.025–0.1 mg/kg (over 2–10 min))
	Ibuprofen or other NSAID (10 mg/kg/dose to a max. of 400 mg p.o. q6 h PRN) if platelet count > 50×10^3/μL PRN and no history of GI bleeding	Ketamine (adjunct to prevent or manage potential uncontrolled pain) as per institutional expert recommendations and policy and procedures related to route and dosing administration
	Morphine sulfate (i.v. bolus 0.05 mg/kg) or alternate medication such as hydromorphone or fentanyl followed by NCA or PCA infusion of morphine, hydromorphone, or fentanyl started 1 h before the infusion of dinutuximab and continued for ≤ 2 h after the end of infusion	Acetaminophen 10–15 mg/kg p.o. q4–6h PRN (max. 650 mg/dose)
	Consider lidocaine if history of pain inadequately managed with opioids	Benzodiazepines (lorazepam): i.v. 0.01–0.02 mg/kg (max. 1 mg) PRN may also be administered before naxitamab infusion
	Acetaminophen 10–15 mg/kg p.o. q4–6h PRN (max. 650 mg/dose)	
Hypotension	Prehydration with 0.9% normal saline 10 mL/kg as an i.v. infusion over 1 h just before initiating each dinutuximab infusion	Prehydration with 0.9% normal saline 10 mL/kg as an i.v. infusion over 1 hour just before initiating each naxitamab infusion
		Some institutions administer a normal saline bolus at the start of each naxitamab infusion

Table 3 (continued)

AE category	Dinutuximab	Naxitamab
Allergic reaction/ hypersensitivity	Antihistamines: 30 min prior (e.g., hydroxyzine, diphenhydramine, or cetirizine)	Antihistamines: 30 min prior (e.g., hydroxyzine, diphenhydramine or cetirizine)
	Hydroxyzine p.o. only:	Hydroxyzine p.o. only:
	< 6 years: 50 mg/day	< 6 years: 50 mg/day
	> 6 years: 50–100 mg/day	> 6 years: 50–100 mg/day
	Diphenhydramine:	Diphenhydramine:
	0.5–1 mg/kg up to a max. dose of 50 mg i.v. over 10–15 min	2–6 years: 6.25 mg p.o. q4–6 h up to a max. dose of 37.5 mg/day
	Cetirizine PRN:	6–12 years: 12.5–25 mg p.o. q4–6 h up to a max. dose of 150 mg/day
	6 months to < 2 years: 2.5 mg p.o. q.d.	>12 years: 25–50 mg p.o. q4–6 h up to a max. dose of 300 mg/day
	2–5 years: 2.5–5 mg p.o. q.d. or 1.25–2.5 mg p.o. b.i.d.	Cetirizine PRN:
	> 5 years: 5–10 mg p.o. q.d. or 2.5–5 mg p.o. b.i.d.	6 months to < 2 years: 2.5 mg p.o. q.d.
		2–5 years: 2.5–5 mg p.o. q.d. or 1.25–2.5 mg p.o. b.i.d.
		> 5 years: 5–10 mg p.o. q.d. or 2.5–5 mg p.o. b.i.d.
		PPI or H_2 antagonist 30 min prior, i.e., famotidine (dose to be determined by institutional recommendation or at the discretion of the treating physician)
		Corticosteroids:[b] e.g. methylprednisolone i.v. 2 mg/kg to max. 80 mg 30–120 min pre-infusion; only on cycle 1 day 1; can be given before subsequent doses if clinically indicated (e.g. if Grade 3 bronchospasm/ anaphylaxis experienced)
Fever	Acetaminophen: 10–15 mg/kg (max. 650 mg/dose) p.o. q4–6 h PRN; give dose before each infusion and then q4 h or q6 h as antipyretic	Acetaminophen: 10–15 mg/kg (max. 650 mg/dose) p.o. q4–6 h PRN; give dose 30 min before each infusion and then q4 h or q6 h as antipyretic
	Ibuprofen PRN (provided platelets > 50×10^3/μL and no history of GI bleeding): 10 mg/kg/dose (max. 400 mg) p.o. q6 h PRN	Ibuprofen PRN (provided platelets > 50×10^3/μL and no history of GI bleeding): 10 mg/kg/dose (max. 400 mg) p.o. q6 h PRN
GI effects	Antiemetic: e.g., ondansetron PRN: 5 mg/m^2/dose (max. 8 mg) i.v./p.o. q8 h PRN	Antiemetic: e.g. ondansetron 5 mg/m^2/dose (max. 8 mg) i.v./p.o. q8 h PRN: give dose 30 min pre-infusion
During infusion[a]		
Pain	Morphine sulfate: i.v. 0.02–0.05 mg/kg/h; additional morphine 0.02–0.05 mg/kg i.v. doses PRN ≤ q2h; or ketamine infusion, fentanyl, or hydromorphone as per patient history or institutional preference and protocols	For breakthrough pain: morphine sulfate (i.v. 0.025–0.1 mg/kg) or hydromorphone (i.v. 0.00375–0.015 mg/kg) as a push bolus every 5 min PRN (max. four doses or treating oncologist discretion)
	Consider NCA or PCA	Ketamine (adjunct to prevent or manage potential uncontrolled pain) as per institutional expert recommendations and policy and procedures related to route and dosing administration
	Consider lidocaine or increase gabapentin dose if pain inadequately managed	Additional repeat dosing of medications noted above pending patient response and tolerance during infusion

Table 3 (continued)

AE category	Dinutuximab	Naxitamab
	Acetaminophen/ibuprofen	
	Non-pharmacologic strategies such as heat/cold therapy; age-appropriate distraction (e.g., comfort and support by parents, play, and use of distraction objects); animal therapy; meditation; hypnosis; music therapy; massage therapy; environmental lighting; noise and conversation levels; guided imagery; and comfort items (e.g., soft toys, blanket)	
Hypotension	Minor hypotension can be managed with hydration (0.9% normal saline: i.v. bolus; 20 mL/kg over 5–15 min) with dinutuximab infusion rate reductions (by 50%) or pauses until BP is within normal limits	Minor hypotension can be managed with hydration (0.9% normal saline: i.v bolus; 20 mL/kg over 5–15 min) with naxitamab infusion rate reductions (by 50%) or pauses until BP is within normal limits
	Inotropes/vasopressors	Moderate or severe reduction in BP requires immediate infusion pause and urgent rescue with aggressive rapid fluid resuscitation during naxitamab infusion
	PRBC transfusion or albumin transfusion if showing signs of capillary leak and/or low hemoglobin and albumin	Inotropes/vasopressors
Allergic reaction/ hypersensitivity	Antihistamines should be infused for 10–15 min q6 h during the dinutuximab infusion	If clinically indicated during naxitamab infusion, consider administration of i.v. antihistamine, i.m. epinephrine 0.01 mg/kg (max. 0.5 mg), and/or inhaled albuterol (< 20 kg: 2.5 mg; >20 kg: 5 mg) ± inhaled epinephrine
	Epinephrine (i.v./i.m.)	Diphenhydramine can be used as rapid rescue in 0.5 mg/kg i.v. aliquots (max. 2 doses)
	Hydrocortisone (i.v. 2 mg/kg)	Hydrocortisone (i.v. 2 mg/kg)
	Nebulizers (levalbuterol and racepinephrine)	Nebulizers (levalbuterol and racepinephrine)
	Albuterol (inhaler) can be considered for severe reactions: bronchospasm, angioedema, anaphylaxis	Topical antihistamine (dexchlorpheniramine)
	Topical antihistamine (dexchlorpheniramine)	
Fever	Draw central blood culture and start antibiotics as indicated	Draw central blood culture and antibiotics as indicated
	Acetaminophen/ibuprofen	Acetaminophen/ibuprofen
GI effects	Antiemetic: e.g., ondansetron 5 mg/m^2/dose (max. 8 mg) i.v./p.o. q8 h PRN	Antiemetic: e.g. ondansetron 5 mg/m^2/dose (max. 8 mg) i.v./p.o. q8 h PRN
Post-infusion[a]		
Pain	Morphine sulfate: i.v. 0.02–0.05 mg/kg/h continued for 2 h following completion of dinutuximab infusion	Acetaminophen 10–15 mg/kg (max. 650 mg/dose) p.o. q4-6h PRN
	Gabapentin p.o. 5–10 mg/kg/dose (max. 300 mg/dose) t.i.d	Gabapentin p.o. 5–10 mg/kg (max. dose of 600 mg/dose) t.i.d: helpful to continue 3 days post-cycle until naxitamab is mostly eliminated from body
	Acetaminophen: 10–15 mg/kg (max. 650 mg/dose) p.o. q6 h PRN	Oral opioid: e.g., oxycodone, hydromorphone, methadone
	Ibuprofen PRN (provided platelets > 50 × 10^3/μL and no history of GI bleeding): 10 mg/kg/dose (max. 400 mg) p.o. q6 h PRN	Ibuprofen PRN (provided platelets > 50 × 10^3/μL and no history of GI bleeding): 10 mg/kg/dose (max. 400 mg) p.o. q6 h PRN
	Oral opioids for pain management post discharge if patient experiencing residual pain	

Table 3 (continued)

AE category	Dinutuximab	Naxitamab
Hypertension	Antihypertensive medication may be prescribed at the treating physician's discretion	
Fever	Acetaminophen Ibuprofen Central blood cultures and antibiotics as indicated	
GI effects	Antiemetic: e.g., ondansetron 5 mg/m^2/dose (max. 8 mg) i.v./p.o. q8 h PRN	

b.i.d. twice daily, *BP* blood pressure, *GD2* disialoganglioside-2, *GI* gastrointestinal, *i.m.* intramuscular, *i.v.* intravenous, *max.* maximum, *min* minute, *NCA* nurse-controlled analgesia, *NSAID* non-steroidal anti-inflammatory drugs, *PCA* patient-controlled analgesia, *p.o.* oral, *PPI* proton pump inhibitor, *PRBC* packed red blood cells, *PRN* pro re nata (as needed; ready at bedside), *q2/4/6/8h* once every 2/4/6/8 h, *q.d.* once daily, *t.i.d.* three times a day

[a] All supportive therapies listed are recommendations that may differ based on institutional policies and preferences

[b] Corticosteroids to be administered before the first infusion and subsequent infusions of naxitamab if a severe infusion reaction occurred with the previous infusion or during the previous cycle

specialists' assessment may assist in the choice of methods, such as heat/cold therapy, age-appropriate distraction (e.g., comfort and support from parents, play, use of distraction objects, animal therapy), meditation, hypnosis, music therapy, massage therapy, environmental lighting, noise and conversation levels, guided imagery, and comfort items (e.g., soft toys, blanket).

In young patients experiencing their first anti-GD2 mAb infusion, pain can lead to breath-holding, which can exacerbate hypoxia. Patients should be encouraged to take deep breaths, and a cold pack can be applied to the back of the neck to help stimulate breathing. If hypoxia does not improve with these measures, humidified oxygen inhalation equipment is recommended.

4.2 Hypotension

Signs of hypotension often develop shortly after the start of the anti-GD2 infusion but may also occur within 24 h of the infusion [9, 12]. Normal saline at 10 mL/kg can be infused 1 h before the dinutuximab or naxitamab infusion to reduce the risk of hypotension [9, 12]. Patients should be laid flat or in the Trendelenburg position if hypotensive. Minor hypotension during anti-GD2 infusions may be managed with hydration and infusion rate reductions or pauses until BP reaches normal limits. However, as moderate or severe hypotension can result in hemodynamic changes, poor perfusion, and a decreased level of consciousness, a more urgent response is required. The infusion should be paused/interrupted and the use of vasopressors such as i.v. or i.m. epinephrine should be considered for hypotension refractory to fluid resuscitation, or if the patient becomes unresponsive to physical stimuli. Additionally, opioid reversal with naloxone and/or possible admission to the intensive care unit should be considered if the patient does not respond to the above interventions.

In addition to the general measures for treating hypotension outlined above, the following specific actions are recommended for dinutuximab and naxitamab. The risk of hypotension is greatest at the start of dinutuximab infusion due to pretreatment with opioids and diphenhydramine. If a patient's BP decreases > 20% below baseline or to below the fifth percentile per age and height [26], the attending team should pause the dinutuximab infusion, and initiate a normal saline bolus of 10–20 mL/kg. Furthermore, the team should closely monitor BP and other vital signs and consider decreasing the opiate dose. If hypotension persists, an additional fluid bolus can be administered; however, if the patient requires multiple fluid boluses, consultation with a rapid response team should be considered. Once significant hypotension is resolved, dinutuximab may be resumed at 50% of the previous rate. If BP is stable for 2 h after

restarting dinutuximab, returning to full rate can be considered. Otherwise, extending subsequent infusions to 20 h is recommended.

Before starting the naxitamab infusion, the patient should be lying supine. In addition to the recommended saline pretreatment, a saline infusion can be given during the first 15 min of the naxitamab infusion before signs of hypotension occur; further hydration can be given after this time, if required. If a patient develops Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. [27] Grade 2 or greater hypotension during the infusion, the attending team may place the patient in Trendelenburg position, administer a normal saline bolus of 10–20 mL/kg, and assess vital signs frequently. The naxitamab infusion rate can be decreased or paused, if clinically indicated. If a patient develops Grade 3 hypotension with other signs/symptoms or Grade 4 hypotension, the naxitamab infusion should immediately be paused and aggressive fluid resuscitation initiated. Close monitoring of the patient and frequent assessment of vital signs should be continued. If hypotension resolves to Grade 2 or less and clinical judgement indicates it is appropriate, the naxitamab infusion can be resumed at 50% of the previous infusion rate. If the patient remains hypotensive and is difficult to arouse, naloxone and/or vasopressor administration should be considered. If the hypotension persists after these measures, the naxitamab infusion should be stopped and the rapid response team consulted.

4.3 Hypersensitivity/Allergy

Patients should be closely monitored for signs of IRRs, such as cough, bronchospasm, hypoxia, angioedema, anaphylaxis, pruritus, and urticaria [3, 9, 10, 12, 24]. Depending on institutional protocols, premedication could include diphenhydramine, hydroxyzine, or cetirizine, depending on patient age, and an H2 antagonist (e.g., famotidine) 30 min before starting the infusion. As the treatment duration is longer with dinutuximab, antihistamines should be infused for 10–15 min, 30 min before the dinutuximab infusion, then every 6 h during the infusion. Suggested doses are shown in Table 3. Patients receiving naxitamab should be premedicated with i.v. corticosteroids before the start of their first infusion in treatment cycle 1 (30–120 min pre-infusion), and before subsequent infusions if a severe IRR occurred during the previous infusion or cycle (Table 3) [9].

Rash, pruritus, and urticaria are also associated with anti-GD2 mAb infusions [9, 12]. Pruritus during infusions can be managed by applying local treatment such as colloidal oatmeal lotion, other non-alcohol-based skin lotions, topical antihistamine, or by administering oral or i.v. antihistamine (e.g., dexchlorpheniramine); occasionally, cold application may be sufficient to relieve symptoms. Small bolus doses of i.v. diphenhydramine can be given during naxitamab infusions for urticaria and/or pruritus if required; however, caution is needed to balance possible hypotensive effects of diphenhydramine. If rash worsens, decreasing the infusion rate to 50%, or pausing it and escalating care as appropriate, should be considered.

Dinutuximab and naxitamab can also cause angioedema, most evident around the lips, tongue, face, eyes, hands, and feet. Mild angioedema can be monitored and does not require intervention. If Grade 2 angioedema occurs, reduce the infusion rate to 50% and monitor closely until it resolves (≤ Grade 1); antihistamines can be considered for moderate to severe angioedema. If angioedema is compromising the airway, pause the infusion, consider i.v./i.m. epinephrine and escalate care appropriately to maintain oxygenation and perfusion.

If the patient develops bronchospasm and stridor during the infusion, administer oxygen and a nebulized bronchodilator or epinephrine. If Grade 2 bronchospasm occurs, reduce the infusion rate to 50% and monitor closely until it resolves (≤ Grade 1). If the patient remains hypoxic, pause the infusion and switch to a non-rebreather face mask. Once bronchospasm, stridor, and hypoxia resolve, the infusion can be restarted at half rate with careful monitoring of the patient. If hypoxia continues, consider i.v./i.m. epinephrine, manual ventilation, and escalating care by consulting the rapid response team. The infusion should not be restarted the same day.

For life-threatening reactions, such as anaphylaxis, the infusion should be stopped immediately; i.v./i.m. epinephrine should be administered straight away, followed by supportive care to maintain airway, perfusion, and oxygenation, as previously described. The rapid response team should be consulted, and supportive medications should be given, such as an i.v. corticosteroid and i.v. antihistamine.

4.4 Hypertension

Patients with uncontrolled hypertension should be treated according to institutional guidelines to ensure their BP is normalized before the infusion starts. Reversible posterior leukoencephalopathy syndrome (RPLS) is a rarely occurring complication of hypertension that was observed during the initial phase 1/2 trial of naxitamab [9] and has occurred in patients treated with dinutuximab [12]. The infusion should be permanently discontinued if signs or symptoms of RPLS develop [9, 12]. To minimize the risk of RPLS, BP should be monitored during and following the anti-GD2 infusion and an assessment for neurologic symptoms should be carried out. As hypertension can be a delayed AE of naxitamab, it is recommended to monitor patient's BP for 72 h post-infusion and teach caregivers how to monitor BP at home.

Antihypertensive medication may be prescribed at the treating physician's discretion post-naxitamab infusion. It is recommended that patients be admitted to an inpatient service for monitoring and management if their BP is ≥ 99th percentile [26]. Discontinuation of either dinutuximab or naxitamab should be considered in patients with persistent hypertension that does not resolve before future infusions despite use of antihypertensive medications.

5 Discussion

Caring for patients receiving dinutuximab or naxitamab treatment can be complex as both can cause signifcant AEs. It is essential that nurses are aware of differences in AE presentation between anti-GD2 mAbs so that appropriate AE management strategies are followed. This ensures that most patients can carry on with subsequent anti-GD2 infusions and their normal activities after discharge without any prolonged AEs, such as severe pain, hypertension, nausea, vomiting, headache, or recurrent cough.

A nurse-centered multidisciplinary team facilitates consistency of care and enables both an individualized treatment approach for each patient and teaching of patients and caregivers. This review can guide nurses to develop their own resources or algorithms for management of a given AE during dinutuximab or naxitamab treatment and provide patients with the best possible care.

We hope that sharing our experiences of AE management for each mAb will benefit other nurses treating patients with dinutuximab or naxitamab, because managing AEs associated with one drug does not necessarily translate to successful management of AEs with the other.

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References

1. Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. Lancet. 2007;369:2106–20. https://doi.org/10.1016/S0140-6736(07)60983-0.
2. Whittle SB, Smith V, Doherty E, Zhao S, McCarty S, Zage PE. Overview and recent advances in the treatment of neuroblastoma. Expert Rev Anticancer Ther. 2017;17:369–86. https://doi.org/10.1080/14737140.2017.1285230.
3. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2 and isotretinoin for neuroblastoma. N Engl J Med. 2010;363:1324–34. https://doi.org/10.1056/NEJMoa0911123.
4. Mora J, Castañeda A, Gorostegui M, Santa-María V, Garraus M, Muñoz JP, et al. Naxitamab combined with granulocyte-macrophage colony-stimulating factor as consolidation for high-risk neuroblastoma patients in complete remission. Pediatr Blood Cancer. 2021;68: e29121. https://doi.org/10.1002/pbc.29121.
5. Cheung NK, Lazarus H, Miraldi FD, Abramowsky CR, Kallick S, Saarinen UM, et al. Ganglioside GD2 specific monoclonal antibody 3F8: a phase I study in patients with neuroblastoma and malignant melanoma. J Clin Oncol. 1987;5(9):1430–40.
6. Modak S, Cheung NKV. Disialoganglioside directed immunotherapy of neuroblastoma. Cancer Invest. 2007;25:67–77. https://doi.org/10.1080/07357900601130763.
7. Mody R, Naranjo A, Van Ryn C, Yu AL, London WB, Shulkin BL, et al. Irinotecan–temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial. Lancet Oncol. 2017;18:946–57. https://doi.org/10.1016/s1470-2045(17)30355-8.
8. Ladenstein R, Pötschger U, Valteau-Couanet D, Luksch R, Castel V, Yaniv I, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19:1617–29. https://doi.org/10.1016/s1470-2045(18)30578-3.
9. Danyelza® (naxitamab-gqgk). Prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761171lbl.pdf. Accessed 28 Jul 2021.
10. Kushner BH, Cheung IY, Modak S, Basu EM, Roberts SS, Cheung NK. Humanized 3F8 anti-GD2 monoclonal antibody dosing with granulocyte-macrophage colony-stimulating factor

in patients with resistant neuroblastoma: a phase 1 clinical trial. JAMA Oncol. 2018;4:1729–35. https://doi.org/10.1001/jamaoncol.2018.4005.
11. Morgenstern DA, Mora J, Chan GC, Nysom K, Bear M, Dalby LW, et al. 74P Pivotal trial 201 data on outpatient administration of naxitamab (Hu3F8), a humanized GD2 targeted immunotherapy for the treatment of refractory/relapsed (R/R) high-risk (HR) neuroblastoma (NB). Ann Oncol. 2020;31(Suppl 7):S1448. https://doi.org/10.1016/j.annonc.2020.10.562.
12. Unituxin™ (dinutuximab). Prescribing information. 2020. https://unituxin.com/full-prescribing-information.pdf.
13. Secola R, Marachelian A, Cohn SL, Toy B, Neville K, Granger M, et al. The role of nursing professionals in the management of patients with high-risk neuroblastoma receiving dinutuximab therapy. J Pediatr Oncol Nurs. 2017;34:160–72. https://doi.org/10.1177/1043454216680595.
14. Llanos C, Lopez S, Molero M, Vallespí M. Implantation of a pioneer naxitamab administration unit in a pediatric oncology European hospital. In: Presented at 50th Congress of the International Society of Paediatric Oncology, November 16–19, 2018; Kyoto, Japan. Abstract. https://doi.org/10.1002/pbc.27455.
15. Mazur KA. Neuroblastoma: what the nurse practitioner should know. J Am Acad Nurse Pract. 2010;22:236–45. https://doi.org/10.1111/j.1745-7599.2010.00503.x.
16. Blom T, Lurvink R, Aleven L, Mensink M, Wolfs T, Dierselhuis M, et al. Treatment-related toxicities during anti-GD2 immunotherapy in high-risk neuroblastoma patients. Front Oncol. 2021;10: 601076. https://doi.org/10.3389/fonc.2020.601076.
17. Bartholomew J, Washington T, Bergeron S, Nielson D, Saggio J, Quirk L. Dinutuximab: a novel immunotherapy in the treatment of pediatric patients with high-risk neuroblastoma. J Pediatr Oncol Nurs. 2017;34:5–12. https://doi.org/10.1177/1043454216659448.
18. Ding YY, Panzer J, Maris JM, Castañeda A, Gomez-Chiari M, Mora J. Transverse myelitis as an unexpected complication following treatment with dinutuximab in pediatric patients with high-risk neuroblastoma: A case series. Pediatr Blood Cancer. 2018;5: e26732. https://doi.org/10.1002/pbc.26732.
19. Sait S, Modak SI. Anti-GD2 immunotherapy for neuroblastoma. Expert Rev Anticancer Ther. 2017;17:889–904. https://doi.org/10.1080/14737140.2017.1364995.
20. Tong W, Maira M, Gagnon M, Saragovi HU. Ligands binding to cell surface ganglioside GD2 cause Src-dependent activation of N-methyl-D-aspartate receptor signaling and changes in cellular morphology. PLoS ONE. 2015;10:e0134255. https://doi.org/10.1371/journal.pone.0134255.
21. Bertolizio G, Otis A, Tam K, Aswar S, Garbin M, Ingelmo P. Multimodal analgesic plan for children undergoing chimeric 14.18 immunotherapy. Pediatr Hematol Oncol. 2021;43:e169–72. https://doi.org/10.1097/mph.0000000000001722.
22. Featherly J, Wojnowicz SB, Steidl K, Burgess J. Lidocaine for dinutuximab-associated pain? A multicenter retrospective observational cohort study. Pediatr Blood Cancer. 2022;2022:e29653.
23. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Shear T, et al. Intraoperative methadone for the prevention of postoperative pain: a randomized, double-blinded clinical trial in cardiac surgical patients. Anesthesiology. 2015;122:1112–22. https://doi.org/10.1097/aln.0000000000000633.
24. Mora J, Chan GC, Morgenstern DA, Nysom K, Bear MK, Tornøe K, et al. Outpatient administration of naxitamab in combination with granulocyte-macrophage colony-stimulating factor in patients with refractory and/or relapsed high-risk neuroblastoma: management of adverse events. Cancer Rep (Hoboken). 2022;2022:e1627.
25. Mora J, Chamizo A, Lazaro JJ, Chamorro S, Lopez-Miralles S, Castañeda A, et al. Ketamine based management of naxitamab (Hu3f8) induced pain in the outpatient setting at HSJD. In: Presented at Annual Neuroblastoma Research Congress, online; Jan 25–27, 2021. https://www.anr2022.org/resources/uploads/sites/26/2021/01/Abstract-book-poster-submissions.pdf.
26. National Heart, Lung and Blood Institute. Blood Pressure levels for boys by age and height percentile. https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf. Accesse 14 Jul 2021.
27. National Cancer Institute. Common terminology criteria for adverse events (CTCAE), Version 5.0. 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 14 Jul 2021.