Dinutuximab

Neuroblastoma Treatment Protocol At KHSC

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June 2nd, 2021

Objectives

By the end of this presentation, participants will be able to:

1. Describe the Basic Principles of Neuroblastoma
2. Discuss the Evidence Surrounding Treatment Protocols for Neuroblastoma
3. Describe the Mechanism of Action of Dinutuximab and Side Effect Profile
4. Highlight the Evidence Surrounding Pain Management Strategies During Infusion
5. Discuss Dinutuximab Use at KHSC Including Pathways and Order Sets

Neuroblastoma

- Embryonal malignancy originating from neural crest tissue of the sympathetic nervous system
- Category encompasses ganglioneuroma, ganglioneuroblastoma and neuroblastoma
- Second most common solid neoplasm in childhood
  - NB accounts for 8-10% of all pediatric cancers
  - Most common solid tumour in children < 1 year old
  - Incidence 10.5/million children/year (650 cases in NA annually)

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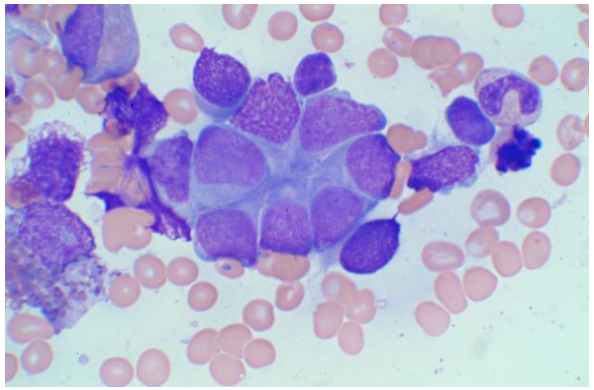
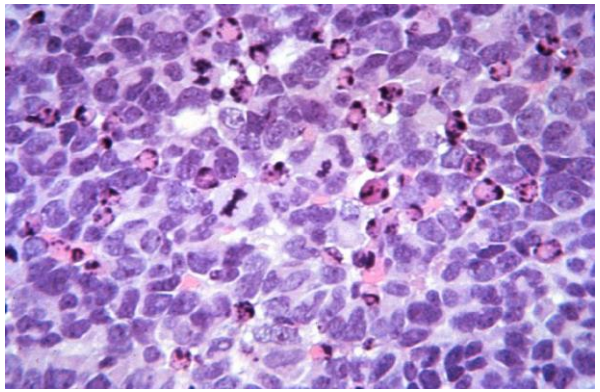
Neuroblastoma

- Small, round and blue tumour cells
- Ganglioneuroma, ganglioneuroblastoma, neuroblastoma:
  - Varying degree of neuronal maturation
  - Homer-wright rosette patterns: tumour cells around neuropil
  - Varying degree of Schwannian stroma intermixed with tumour cells
  - Varying degree of mitosis and karyorrhexis



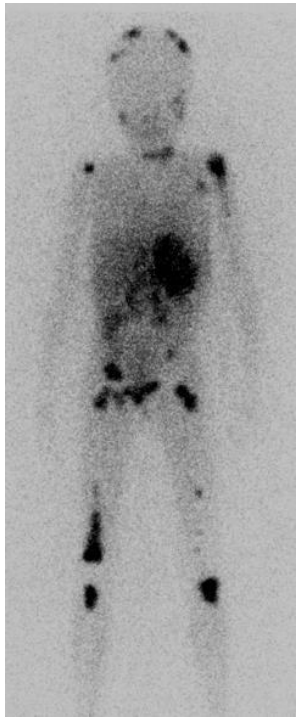


Neuroblastoma – Clinical Presentation

Incidental finding (MOST COMMON)	No symptoms
Associated with primary site or nodal metastatic disease	Neck mass Abdominal distension Horner syndrome GU symptoms Neurologic abnormalities (paralysis) Hypertension
Associated with metastatic disease	Ill appearing, fever Malaise, irritability Weight loss, anorexia Skin nodules
Bone or marrow metastases	Pain: ill defined (40%) Proptosis
Respiratory distress	Restrictive disease due to liver enlargement/mass Effusions
Paraneoplastic syndromes	Vasoactive intestinal polypeptide (secretory diarrhea) Opsoclonus Myoclonus

Neuroblastoma – Diagnosis & Staging

- Elevated serum or urine catecholamines metabolites (HVA/VMA)
- Peripheral blood counts, renal function, liver function/coagulation studies
- CT/MRI (primary and nodal metastatic sites)
- Radiolabelled-MIBG (I-123)
  - FDG PET if tumour is MIBG non-avid (~10%)
- Tumour biopsy
- Bilateral bone marrow aspirates and biopsies



Neuroblastoma – Prognostic Factors

Risk Group	Stage	Age	MYCN	Ploidy	Shimada
Low Risk	1	any	any	any	any
Low Risk	2a/2b	any	not amp	any	any
High Risk	2a/2b	any	amp	any	any
Intermediate Risk	3	<547d	not amp	any	any
Intermediate Risk	3	>547d	not amp	any	FH
High Risk	3	any	amp	any	any
High Risk	3	>547d	not amp	any	UH
High Risk	4	<365d	amp	any	any
Intermediate Risk	4	<365d	not amp	any	any
High Risk	4	365-<547d	amp	any	any
High Risk	4	365-<547d	any	DI=1	any
High Risk	4	365-<547d	any	any	UH
Intermediate Risk	4	365-<547d	not amp	DI>1	FH
High Risk	4	>547d	any	any	any
Low Risk	4s	<365d	not amp	DI>1	FH
Intermediate Risk	4s	<365d	not amp	DI=1	any
Intermediate Risk	4s	<365d	not amp	any	UH
High Risk	4s	<365d	amp	any	any

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Neuroblastoma – Stage 4S/MS

- Localized primary tumour
- Dissemination limited to skin, liver and/or bone marrow
- Favorable biology
- Infants < 12 months (< 18 months?)
- Treatment options:
  - Observation (potential for spontaneous resolution)
  - Chemotherapy if symptomatic or unfavorable biology elements

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Neuroblastoma - Treatment

- Low Risk
  - EFS >90%; OS 99-100%
  - Surgery
  - Chemotherapy (low dose, reserved for symptomatic disease)
  - Observation alone (infants with small Stage 1/L1 adrenal tumours)
- Intermediate Risk
  - EFS>85%; OS >90%
  - Surgery
  - Chemotherapy: multiagent, 2-8 cycles

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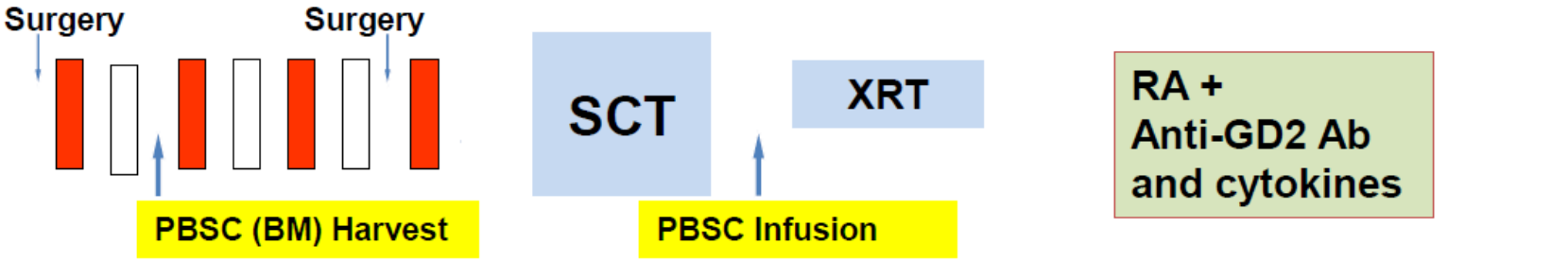
Neuroblastoma – High Risk Treatment

- 5 yr OS 40-50%
- "Kitchen sink therapy"



Induction:
Multi-Agent Chemotherapy;
Stem Cell Collection;
Surgery

Consolidation:
Myeloablative Therapy;
Autologous SCT infusion;
External Beam
Radiotherapy

Post-Consolidation:
Biologic Response
Modifier (isotretinoin=RA);
Immunotherapy

Children's Oncology Group

Neuroblastoma – High Risk Treatment

- Children's Cancer Group (predecessor of the COG)
- 3 yr EFS with HSCT was better than for those who received continuing chemotherapy (34% vs 22%)
- 3 yr EFS with 13-cis-retinoic acid was better than those who did not receive further therapy (46% vs 29%)

The New England Journal of Medicine

VOLUME 341 OCTOBER 14, 1999 NUMBER 16

TREATMENT OF HIGH-RISK NEUROBLASTOMA WITH INTENSIVE CHEMOTHERAPY, RADIOTHERAPY, AUTOLOGOUS BONE MARROW TRANSPLANTATION, AND 13-*CIS*-RETINOIC ACID

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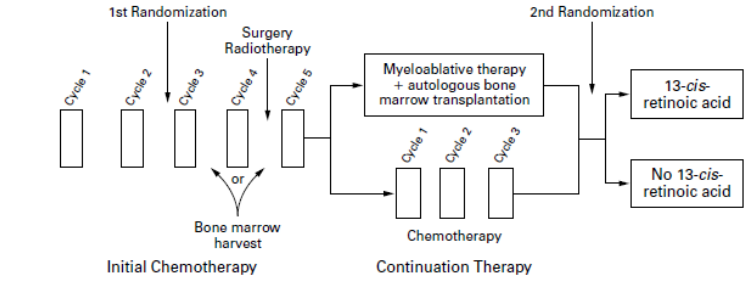

Figure 1. Treatment Regimens.
The conditioning regimen for autologous bone marrow transplantation consisted of carboplatin, etoposide, melphalan, and body irradiation. Details of the chemotherapy regimens are given in the Methods section.

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Neuroblastoma – High Risk Treatment

- COG A3973: 2003-2007
  - Phase III RCT – addition of purged vs non-purged HSCT to chemotherapy/maintenance isotretinoin (no benefit); studied extent of surgical resection needed
- ANBL0032
  - Phase III RCT – addition of Anti-GD2 antibody with GM-CSF, IL-2 and isotretinoin
  - Stopped early because of efficacy of immunotherapy: EFS (66% vs 46% at 2 years) and OS (86% vs 75%)
- ANBL0532
  - Phase III RCT – compare one cycle of HSCT to two cycle
  - Two cycles superior (62% EFS vs 48% EFS)
  - If dinutuximab added as consolidation (73% vs 55%)

Neuroblastoma – High Risk Treatment

Study Goal:

To improve outcomes by integrating targeted therapy (MIBG, ALK inhibition) early in the treatment of children with high risk NBL.

Activated: 05/09/18
Closed:

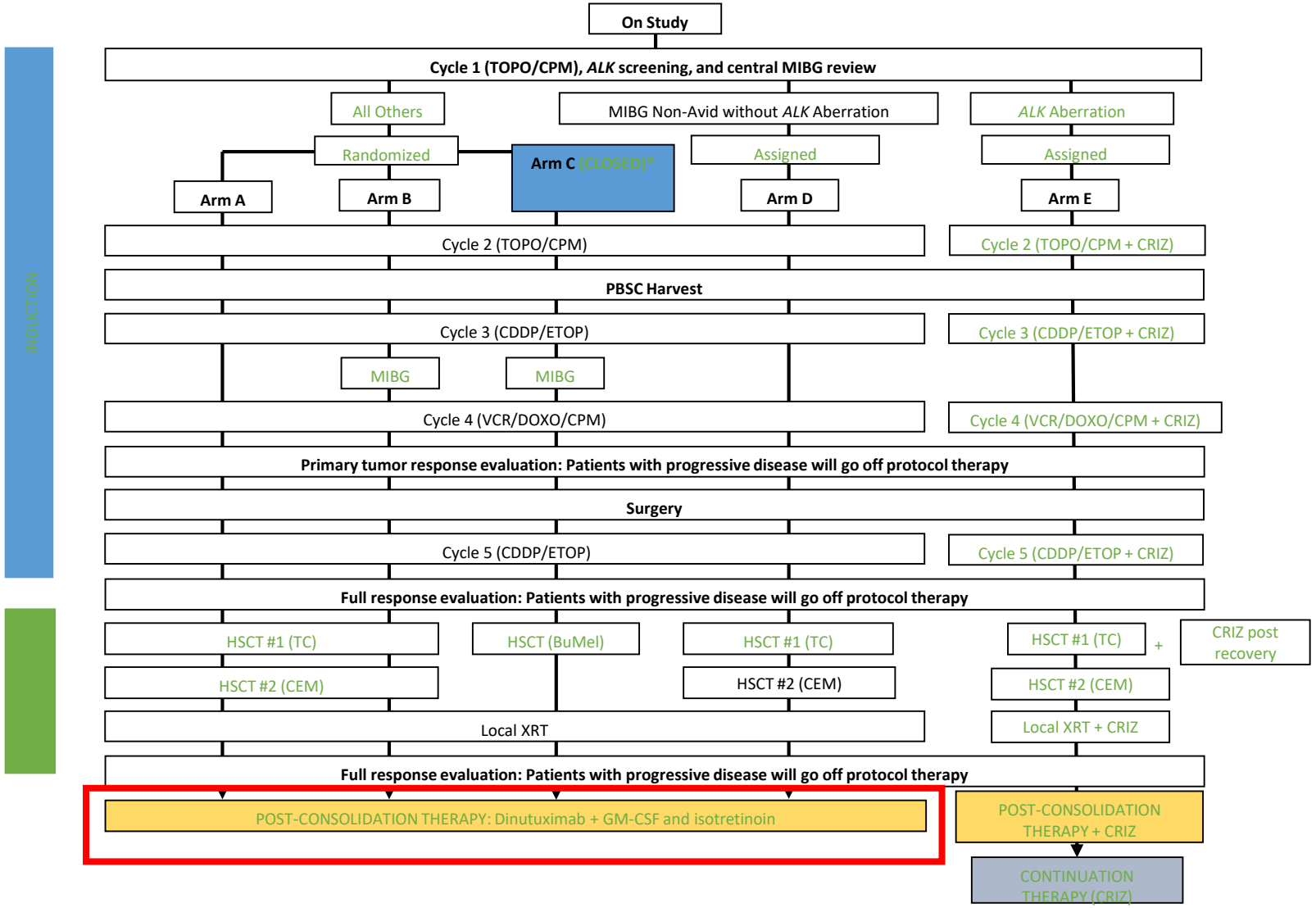
Version Date: 01/22/21
Amendment #7

CHILDREN'S ONCOLOGY GROUP

ANBL1531

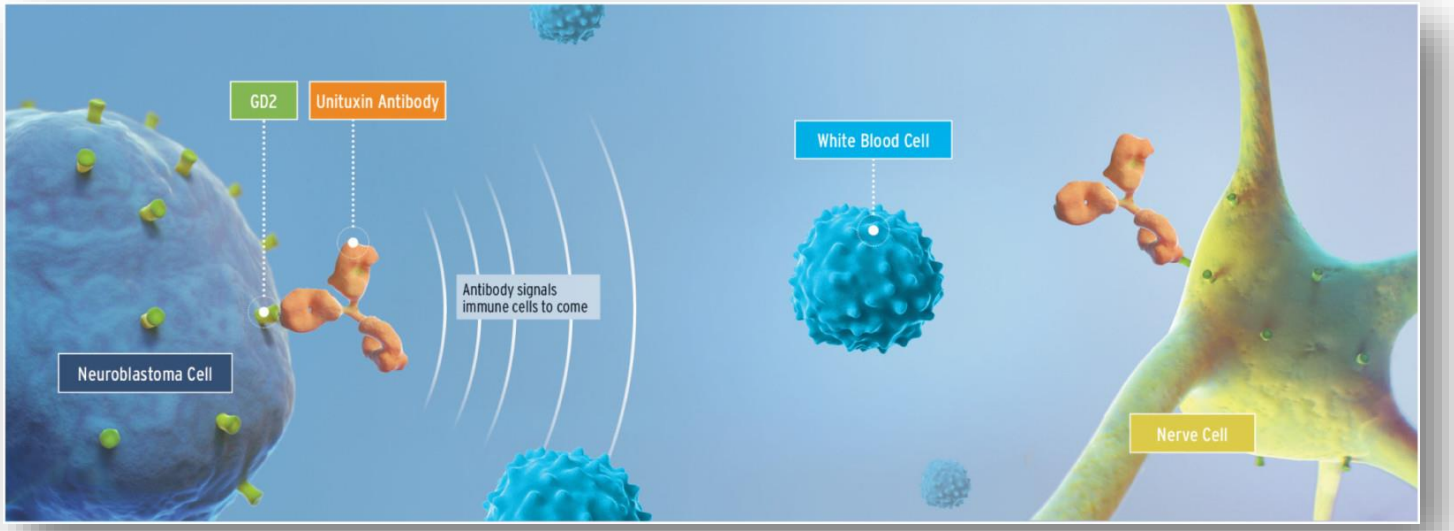
A Phase 3 Study of ^{131}I-Metaiodobenzylguanidine (^{131}I-MIBG) or Crizotinib Added to Intensive Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma (NBL) (IND# 134379)

Neuroblastoma – ANBL1531



Dinutuximab

- Human-murine IgG1 kappa monoclonal antibody that targets glycolipid disialoganglioside (GD2)
- Induces cell lysis via antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity in cells overexpressing GD2



https://unituxin.com/about-unituxin/mechanism-of-action/antibody-therapy/

Side Effects

Toxic Effect	Immunotherapy (N=137)	Standard Therapy (N=108)
	Number of patients (percent)	
Neuropathic Pain ★	71 (52)	6 (6)
Hypotension ★	24 (18)	0
Hypoxia	18 (13)	2 (2)
Fever without neutropenia	53 (39)	6 (6)
Acute Capillary Leak ★	31 (23)	0
Hypersensitivity Reaction ★	34 (24)	1 (1)
Urticaria ★	18 (13)	0
Infection (any)	54 (39)	24 (22)
Nausea	4 (3)	1 (1)
Diarrhea	18 (13)	7 (7)
Hyponatremia	31 (23)	4 (4)
Hypokalemia	48 (35)	2 (2)
Abnormal ALT	31 (23)	3 (3)
Abnormal AST	14 (10)	0
Hypercalcemia	7 (5)	6 (6)
Serum sickness	1 (1)	0
Ocular Symptoms	0	1 (1)

Toxic Effect	Immunotherapy (N=137)	Standard Therapy (N=108)
	Number of patients (percent)	
Seizure	1 (1)	1 (1)
CNS cortical symptoms	5 (4)	0
None	8 (6)	40 (37)

Yu, A.L. et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. New England Journal of Medicine. 362.1324-1334

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Side Effects

Toxic Effects of Grade 3 or 4 in Patients Randomly or Nonrandomly Assigned to Receive Immunotherapy, According to Immunotherapy Cycle.*						
Toxic Effect	Cycle 1 (N=137)	Cycle 2 (N=127)	Cycle 3 (N=121)	Cycle 4 (N=114)	Cycle 5 (N=107)	Cycle 6 (N=104)
	Number of patients (percent)					
Pain ★	50 (37)	30 (24)	23 (19)	33 (29)	15 (14)	4 (4)
Hypersensitivity Reactions	14 (10)	33 (26)	6 (5)	29 (25)	13 (12)	3 (3)
Capillary Leak Syndrome	9 (7)	14 (11)	8 (7)	15 (13)	3 (3)	0

- Pain reactions in immunotherapy group were most frequent during cycle 1, occurring in 37% of patients and decreasing to 14% during cycle 5 ($p<0.001$)[1]
- Severity of pain with subsequent courses have been shown to decrease[1,2]

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Yu, A.L. et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. New England Journal of Medicine. 362.1324-1334

Side Effects

Table 5. Summary of the Published Reports on ch14.18

First Author	Therapy	Tumor Type and No. of Patients	Toxicity	Pharmacology	HACA Positivity (no. of patients)	Response
Saleh[28]	Phase I ch14.18 only	13 with metastatic melanoma	Neuropathic pain	T1/2α 24 $\pm$ 1 hour, T1/2β 181 $\pm$ 73 hours	8/13	No response
Handgretinger[7]	Phase I ch14.18 only	9 with stage IV neuroblastoma	Neuropathic pain, pruritus, urticaria, transient pupillatonia	Not done	0/9	2 CRs, 2 PRs, 1 minor response
Yu[10]	Phase I ch14.18 only	10 with refractory neuroblastoma and 1 with osteosarcoma	Neuropathic pain, tachycardia, hypertension, fever, urticaria	CDC activity against neuroblastoma cells in 5/5 patients	3/8	1 PR, 4 mixed responses
Murray[29]	Phase I ch14.18 + GM-CSF	16 with metastatic melanoma	Neuropathic pain, hypertension, hypotension, headache, nausea, diarrhea, peripheral nerve dysesthesias, myalgias, weakness	T1/2β 123 $\pm$ 29 hours; increased ADCC activity in 10/11 patients	6/16	No response
Yu[27]	Pilot ch14.18 + GM-CSF	17 with refractory neuroblastoma	Neuropathic pain, fever, tachycardia, hypertension, nausea, vomiting, diarrhea, hyponatremia, hypokalemia, urticaria, transient thrombocytopenia	Increased ADCC activity in 5/9 patients	Not done	3 CRs, 1 PR, 2 mixed responses
Yu[30]	Phase II ch14.18 + GM-CSF	32 with refractory neuroblastoma	Neuropathic pain, fever, tachycardia, hypotension, hypertension, nausea, vomiting, diarrhea, hyponatremia urticaria, transient thrombocytopenia	All responding patients had increased ADCC	Not reported	Among 27 available for response: 1 CR, 3 PRs, 1 mixed response
Ozkaynak (current study)	Phase I ch14.18 + GM-CSF immediately post-HSCT	19 with neuroblastoma	Neuropathic pain, fever, nausea, vomiting, urticaria, hypotension, capillary leak syndrome, dilated pupils, diplopia, transient thrombocytopenia	Mean peak ch14.18 level 5,607 ng/mL at 40 mg/m^2/d (MTD)	5/18	Not applicable

Ozkaynak, M. F. et al. Phase I study of chimeric human/murine anti-ganglioside GD2 monoclonal antibody (ch14.18) with granulocyte-macrophage colony-stimulating factor in children with neuroblastoma immdeicatley after hematopoiectic stem-cell transplantation: a children's cancer group study. Journal of Clinical Oncology. (2000) 18(24). 4077-4085.

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Dinutuximab – Side Effects

- Capillary Leak Syndromes:
  - Result of damage to endothelial cells from the immune-mediated, cytotoxic response to Sargramostim (GM-CSF)
  - Increased permeability
  - Symptoms: facial edema, neck vein distension, peripheral edema, dyspnea, crackles on auscultation, pulmonary function derioration, cough, weight gain, hypotension and tachycardia
  - Management: monitor for edema (weights BID, strict I/Os), monitor electrolytes, hemoglobin and albumin; encourage PO intake rather than fluids; albumin, pRBCs and lasix

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Dinutuximab – Side Effects

- Hypotension (more than 15% decrease from baseline):
  - SE of infusion, sign of capillary leak, result of opioids + diphenhydramine
  - Management: close monitoring of blood pressure, NS bolus pre-infusion
- Fever:
  - Expected reaction due to stimulation of immune system and increased cytokines; may also be result of infection
  - Management: cultures, antibiotics (Ceftriaxone), antipyretics (consider ibuprofen)

Dinutuximab – Side Effects

- Infusion related reactions:
  - Result of overstimulation of immune system and release of cytokines
  - Urticaria, transient rash, fever, rigors
  - Severe: bronchospasm, facial and upper airway edema, dyspnea, stridor, hypotension
  - Treatment: antihistamines and antipyretics pre-infusion and routinely throughout

Dinutuximab – Side Effects

- Neuropathic pain:
  - Potentially caused by binding of dinutuximab to the GD2 on normal cells of neuroectodermal origin
  - Occurs during infusion, peaking at 60-90 minutes into the infusion, sudden onset
  - Abdominal, generalized, extremity, back, neuralgia, MSK chest, arthralgia
    - Whole body allodynia, transient neuropathic pain[7]
  - Treatment: gabapentin, narcotic infusions
  - Collaboration with APMS

Dinutuximab and Pain

- Specific binding of Dinutuximab to neurons & peripheral nerve fibers which express GD2[1,2,3,4]
  - Pain of grade 3 or 4 was observe in 52% of patients[1]
    - Ranging from 33-87%
    - Major toxicity was neuropathic pain[8] – 13 (68%) of 19 patients experienced severe pain during the first course of therapy noted within 1 hr of starting ch 14.18 infusion
  - Pain presents similary to neuropathic pain syndromes, however transient and persists duration of ch 14.18 infusion[7]
  - Common site of pain presentation: abdomen > extremity

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Dinutuximab and Pain Management

- Use of opioids for the duration of antibody therapy is essential[2,4]
  - **Child Oncology Protocol**[7] **-** Loading dose 50 mcg/kg, infusion 20-50 mcg/kg/hr
  - Phase I studies[1,8] – severe neuropathic pain necessitated continuous infusion of morphine – observation in 68% of patients during first course – loading dose 50 mcg/kg, infusion 50 mcg/kg/hr
- Providing a bolus dose and continuous infusion of opioid is standard of care[2,3]
  - Infusions started 30-60 minutes prior to initiation of Dinutuximab
  - Stopped 1-2 hrs post infusion
- Subsequent courses, start at highest dose of opioid required for adequate pain control during prior course, including adjuncts [2,3]

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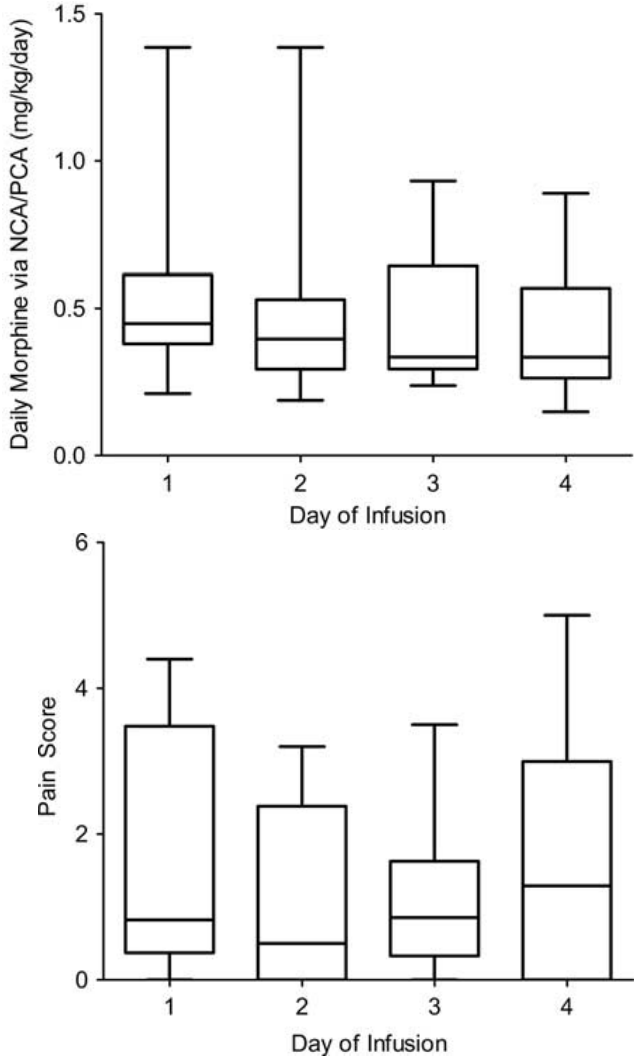
Study	Analgesic Modality	Total Analgesic Consumption	Side Effects Related to Analgesics
Ozkaynak [8]	Morphine 0.1 mg/kg bolus + 0.05 mg/kg/hr	Not listed	Listed for dinutuximab but not isolated for opioid
Wallace[5]	Lidocaine 2 mg/kg + 1 mg/kg/hr OR Morphine 0.1 mg/kg + 0.05-0.1 mg/kg/hr Morphine 0.05 mg/kg q 2 hrs PRN	Average daily lidocaine 170 mg ± 40 mg (8.9 ± 1.1 mg/kg) Morphine consumption represented graphically only –***50-100 mcg/kg/hr or 10-12.5 mg/day***	No significant change in BP Increased HR Increased emesis day 4 – LIDO
Gorges[4]	Hydromorphone 2 - 8 mcg/kg/hr Dexmedetomidine 0.1-0.6 mcg/kg/hr +/- Gabapentin	Median Dose/Treatment day Dexmedetomidine 2.3 mcg/kg/hr or 0.17 mcg/kg/hr; 44.1 mcg/kg/day ***Morphine equivalents = 15-20 mcg/kg/hr or 200-300 mcg/kg/day***	Percentage of treatment days Hypotension – 30 Hypoxemia – 8 Bradycardia - 4
Ari[7]	NCA/PCA Morphine demand dose 0.02-0.04 mg/kg lockout 8 – 20 minutes + basal 0.02-0.04 mg/kd/hr	Mean total daily morphine 0.46 mg/kg/d = ***460 mcg/kg/day*** *(mean daily amounts 0.448, 0.396, 0.335, 0.335 mg/kg/day on days 1-4 respectively)*	No reports of respiratory depression or life-threatening events Hypotension and tachycardia 37%
Bertolizio [9]	Gabapentin 5 mg/kg TID NCA 0.04 mg/kg q 20 min PRN + basal 0.01 mg/kg/hr OR PCA 0.02 mg/kg q 10 min PRN + basal 0.01 mg/kg/hr Ketamine 0.2 mg/kg/hr + 0.2 mg/kg q 4hrs PRN	Daily median morphine consumption ***201 mcg/kg/d*** cycle 1, ***260 mcg/kg/d*** cycle 2, ***290*** mg/kg/d cycle 3 Median hourly morphine consumption ranged from ***17 to 27 to 29 mcg/kg/hr*** Median Ketamine consumption ***0.21 to 0.22 to 0.26 mg/kg/h***	Incidence of desaturations 4.2% - no episodes <90 or respiratory arrest Hypotension 2.3% in cycle 1 to 0.3% in cycle 3 No hallucinations/tachycardia

Opioids

- Case series[7] examining morphine given by NCA-IV or PCA-IV to control ch 14.18 antibody-induced transient pain – Retrospective
  - N=16 children, identified between 2009-2016, average age 4.3 years
- Primary endpoint: total morphine consumption in 24 hrs
- NCA/PCA Morphine dosing: 20-40 mcg/kg q 8-20 min + basal 20-40 mcg/kg/hr
- Results: mean morphine amount was highest on day 1 and progressively decreased throughout 4 day treatment; mean total daily morphine 0.46 mg/kg/day
  - Mean pain scores ranged from 0-5, higher scores reported day 1 + 4
  - Majority of pain scores on any given day ranged between 0 and 1.3



Ari, P. et al. Treatment of Transient Peripheral Neuropathy During Chimeric 14.18 Antibody Therapy in Children with Neuroblastoma: A Case Series. J Pediatr Hematol Oncol (2018).40.e113–e116)

Dexmedetomidine

- Case series of six children receiving ch14.18 therapy, dexmedetomidine was used in conjunction to reduce total opioid consumption
  - Median age 3.5 yrs (2-12 yrs)
- Retrospective Data collection: September 2010 – December 2012 – 29 Immunotherapy sessions
- Intervention: Hydromorphone and Dexmedetomidine both started 1 hr prior to dinutuximab infusion
  - Hydromorphone 0.2 mcg/kg/hr titrated to max 0.8 mcg/kg/hr + Dexmedetomidine 0.1 mcg/kg/hr titrated to 0.6 mcg/kg/hr
  - Stopped 1 hr following cessation of dinutuximab
  - Patient charts were reviewed for evidence of side effects and quality of analgesia

Gorges, M. et al. Dexmedetomidine and Hydromorphone:A novel pain management strategy for the oncology ward setting during anti-GD2 immunotherapy for high-risk neuroblastoma in children. Pediatr Blood Cancer. 2015. 62. 29-34.

Dexmedetomidine

- Results
  - Median (range) utilization of hydromorphone was 2.9 (2.0–4.7) mcg/kg/hr, and of dexmedetomidine was 0.17 (0.10–0.20) mcg/kg/hr
  - Most frequent side effect was hypotension 36/121 (30%) treatment days, hypoxemia 10/122 (8%) treatment days, bradycardia 5/122 (4%) treatment days
- Limitations
  - Missing pain scores
  - No comparison to opioids alone

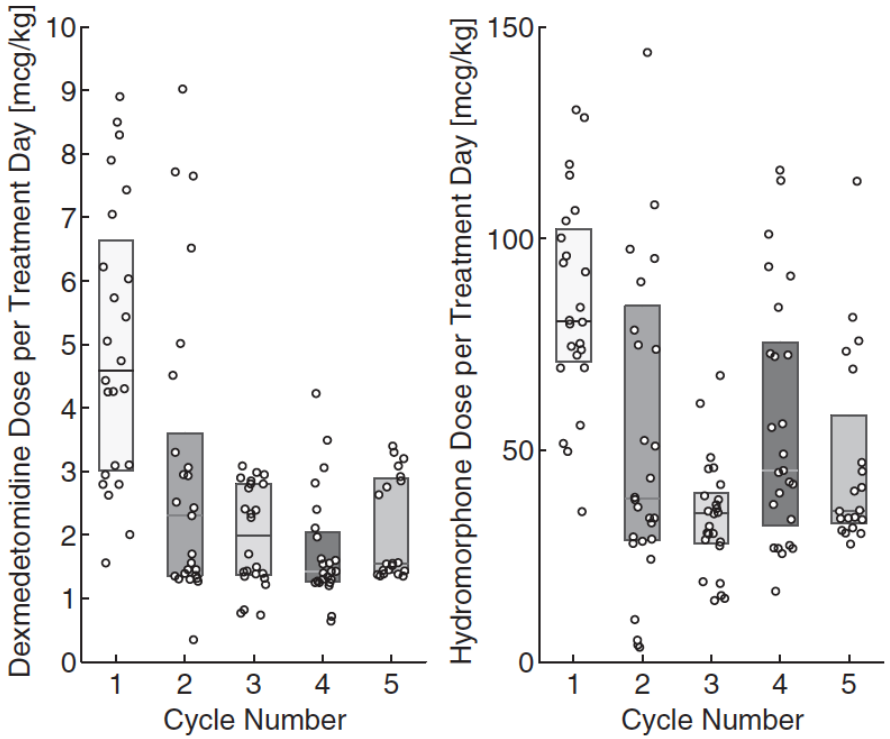


Fig. 1. Dexmedetomidine (left subplot) and hydromorphone (right subplot) doses per treatment day, split by ch14.18 treatment cycle. Each plot shows raw data as a dot plot overlaid with quartile boxes (1st quartile, the median value, and the 3rd quartile).

Gorges, M. et al. Dexmedetomidine and Hydromorphone:A novel pain management strategy for the oncology ward setting during anti-GD2 immunotherapy for high-risk neuroblastoma in children. Pediatr Blood Cancer. 2015. 62. 29-34.

Ketamine

- Retrospective study – first 3 cycles of 6 children undergoing ch 14.18
- Analgesic regimen
  - Gabapentin 5 mg/kg TID from day #1 to day #4 of each cycle + morphine continuous infusion 10 mcg/kg/hr, NCA boluses 40 mcg/kg q 20 min prn / PCA boluses 20 mcg/kg q 10 minPRN + Ketamine 200 mcg/kg/hr
  - Ketamine bolus 0.2 mg/kg q 4 hr PRN
- Endpoints
  - Primary endpoints: mean pain score and incidence of severe pain
  - Secondary Endpoints: consumption of morphine + ketamine, and incidence of adverse effects related to treatment

Bertolizio, G. et al. Multimodal analgesic plan for children undergoing chimeric 14.18 immunotherapy. Journal of Pediatric Hematology/Oncology. (2021).43(2). E169-e172.

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Ketamine

- Results
- Mean Pain Scores ranged between 0.3-0.6
- Highest daily median morphine consumption 0.29 mg/kg/day in cycle 3

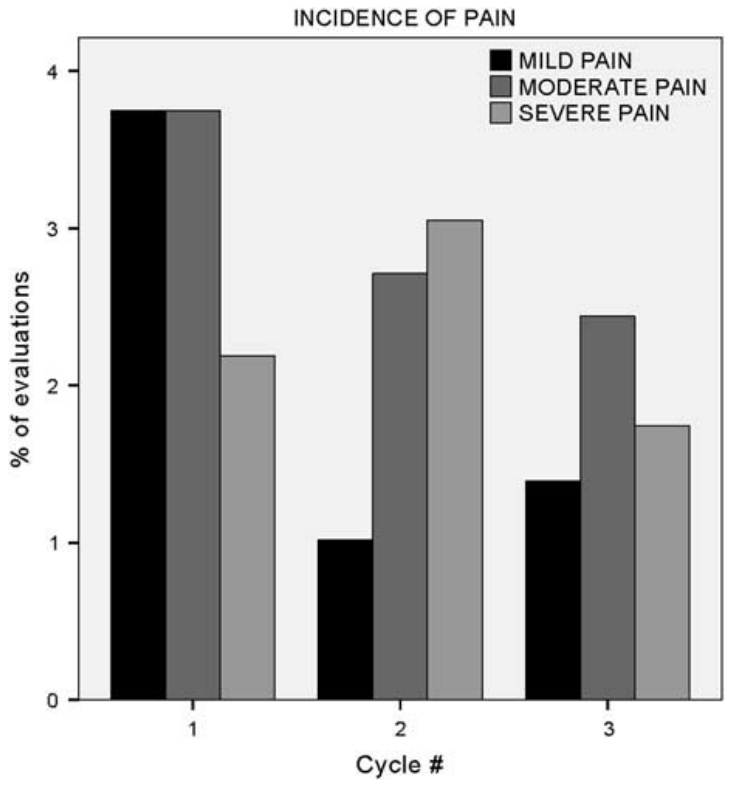

FIGURE 1. Incidence of mild (0 to 3), moderate (4 to 6) and severe pain (7) during the hourly evaluation of each cycle. Overall pain episodes decreased after each cycle.

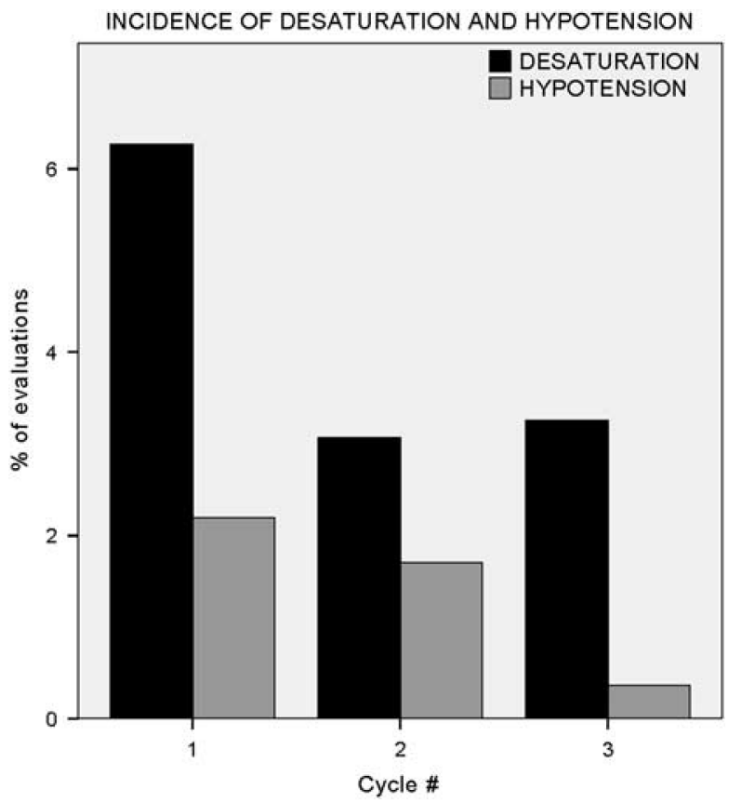

FIGURE 2. Incidence of desaturation (<95%) and hypotension (–20% from baseline) during each cycle.

Bertolizio, G. et al. Multimodal analgesic plan for children undergoing chimeric 14.18 immunotherapy. Journal of Pediatric Hematology/Oncology. (2021).43(2). E169-e172.

Lidocaine

- Case series of five children, median age 4.9 yrs
  - All patients had received morphine infusions for a previous cycle
  - Subjects received either lidocaine 2 mg/kg or morphine 0.1 mg/kg followed by continuous infusion of lidocaine 1 mg/kg/hr or morphine 50-100 mcg/kg/hr respectively
  - Outcomes: Pain scores rated on a scale 1-7 (faces scale) q 2 hours and at completion (7 hrs), morphine consumption and mobility
- Results
  - No significant difference in morphine requirements for breakthrough pain between group, there was much greater total morphine consumption in the morphine group
  - No significant difference in pain scores between groups

Wallace, M. et al. Intravenous lidocaine: effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma – a report of a series. Anesth Analg.(1997). 85.794-796.

Lidocaine

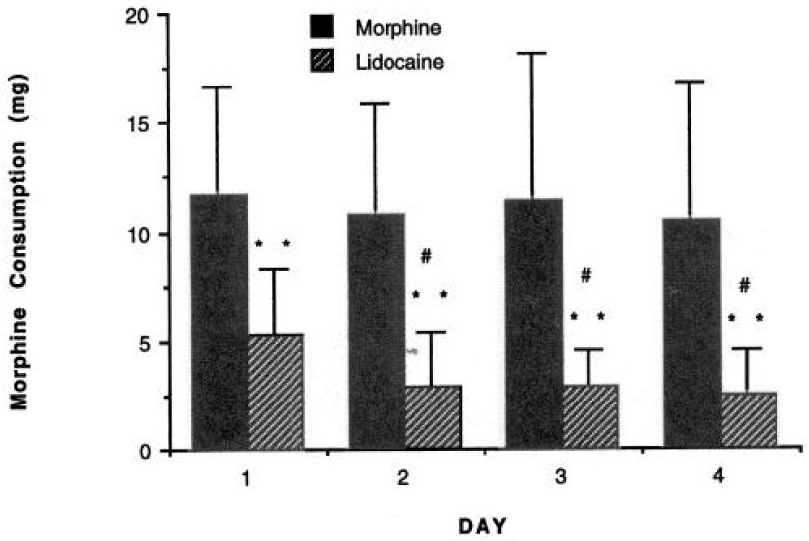

Figure 1. Comparison of daily morphine requirements for pain control in patients receiving an intravenous morphine versus intravenous lidocaine infusion for pain control during anti-GD_2 infusion. $^{**}P < 0.01$ between groups. $\#P < 0.05$ in lidocaine group on Days 2–4 compared with Day 1.

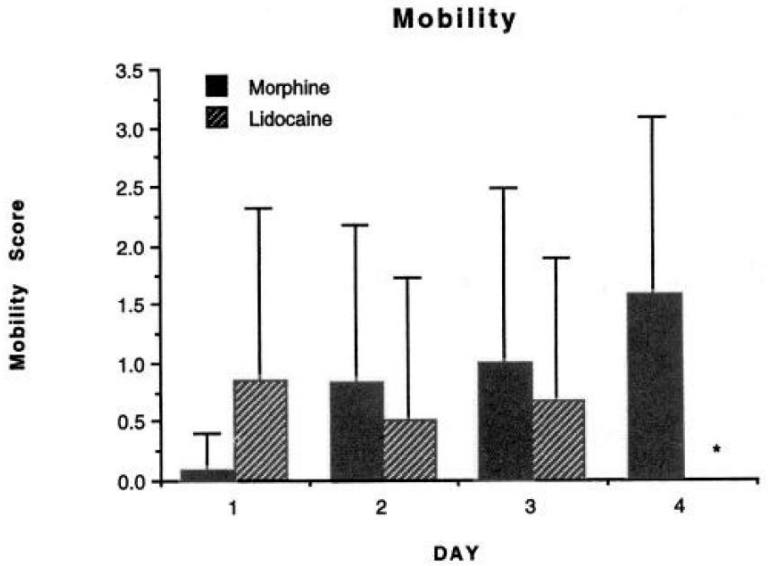

Figure 2. Comparison of daily mobility scores in patients receiving an intravenous morphine versus intravenous lidocaine infusion for pain control during anti-GD_2 infusion. Mobility was scored as follows: ambulating = 0, walking with help = 1, confined to a chair = 2, confined to bed = 3. $^{*}P < 0.05$ between groups.

Wallace, M. et al. Intravenous lidocaine: effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma – a report of a series. Anesth Analg.(1997). 85.794-796.

SICK KIDS Protocol

10 hr Infusion

- Start continuous opioid infusion 1 hr prior to Dinutuximab
- Opioid bolus immediately prior to dinutuximab
- Opioid boluses q2hr PRN throughout infusion
- Stop continous opioid infusion 1 hr following Dinutuximab

20 hr Infusion

- Start continuous opioid infusion 1 hr prior to Dinutuximab
- Opioid bolus immediately prior to dinutuximab
- Opioid boluses q2hr PRN throughout infusion
- Continue continous opioid infusion for 4 day cycle and stop 1-2 hrs following Dinutuximab

SickKids®

BC Children Protocol

Day 1, 1st Cycle

Start continuous hydromorphone / dexmedetomidine infusion 1 hr prior to dinutuximab

↓

hydromorphone 2 mcg/kg/hr

dexmedetomidine 0.2 mcg/kg/hr

↓

Alternate increases of continuous infusions q30 min

↓

Stop dexmedetomidine infusion 1 hr following dinutuximab, wean hydromorphone

Day 2-4 and Subsequent Cycles

Start at doses where they left off prior

↓

If hydromorphone continued, increase to prior rate (20 hr treatments

BC Children's Hospital™

KHSC Dinutuximab Protocol Overview

Escalation of Pain Management and Involvement of APMS

- Suggested ranges for opioid dosing available
- Increase basal continuous infusion & reassess hourly
- Breakthrough opioid q2 hrs PRN – if needing more frequently increase basal
- Calculate bolus dosing into continuous infusion
- Day 2 of cycle and with next cycle – start at escalated dose
- No specific ceiling – usually rotate opioid or add second agent due to side effects or inadequate pain management
  - Opioid rotation
  - + Ketamine infusion
  - + Dexmedetomidine (*needs special permission)*

KHSC Order Set

Pre Medication and Supportive Care

- ☒ Acetaminophen _____ mg *(12.5 mg/kg/dose, maximum 650 mg/dose)* PO 20 minutes prior to each dinutuximab infusion and THEN q 4h.
- ☒ DiphenhydrAMINE _____ mg *(1 mg/kg/dose, maximum 50 mg/dose)* PO or IV prior to first dose of dinutuximab and THEN q 6h.
- ☒ Famotidine _____ mg *(0.25-0.5 mg/kg/dose, maximum 20 mg/dose)* IV prior to first dose of dinutuximab, and THEN q 12h.
- ☒ Ondansetron _____ mg *(5 mg/m^2/dose; maximum 8 mg/dose)* IV/PO prior to starting dinutuximab, and THEN q 8h.
- ☐ Cetirizine _____ mg *(2.5 mg for 6 months to less than 2 years of age, 2.5-5 mg for 2-5 years of age, 5-10 mg for over 5 years of age)* for 1 dose prior to dinutuximab each day. *(For patients with a history of allergic reactions)*
- ☐ Hydroxyzine _____ mg *(0.7 mg/kg/dose; maximum 100 mg/day)* PO tid PRN for rash and/or itchiness.
- ☐ Ibuprofen _____ mg *(10 mg/kg/dose, maximum 600 mg)* PO q 6h PRN for persistent fever or pain. *(only for patients with platelets over 50 X 10^9/L and no history of GI bleeding)*
- ☐ Other _____
- ☐ Other _____

Pain Management

- ☒ Gabapentin _____ mg *(5 mg/kg/dose; maximum of 300 mg/dose)* PO tid. *(Patient should be titrated up to this dose prior to starting dinutuximab)*
- ☒ Morphine _____mg *(0.05 mg/kg/dose)* IV bolus, THEN _____ mcg/kg/h IV infusion *(20 mcg/kg/h usual initial rate; 50 mcg/kg/h usual maximum rate)*
  - ☒ Morphine _____ mg *(0.02 mg/kg/dose)* IV q 2h PRN for breakthrough pain.
- ☐ Hydromorphone _____ mcg/kg/h IV infusion. *(2 mcg/kg/h usual initial rate; 4 mcg/kg/h usual maximum rate)*
- ☐ Ketamine infusion _____ mcg/kg/h IV infusion. *(100 mcg/kg/h usual initial rate; 300 mcg/kg/h usual maximum rate)*
- ☐ Other _____
- ☐ Other _____
- ☒ Notify prescriber if pain requires an increase in narcotic infusion rate

KHSC

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QUESTIONS