Dinutuximab
Neuroblastoma Treatment Protocol At KHSC

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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)
**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

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

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Stage</th>
<th>Age</th>
<th>MYCN</th>
<th>Ploidy</th>
<th>Shimada</th>
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<tbody>
<tr>
<td>Low Risk</td>
<td>1</td>
<td>any</td>
<td>any</td>
<td>any</td>
<td>any</td>
</tr>
<tr>
<td>Low Risk</td>
<td>2a/2b</td>
<td>any</td>
<td>not amp</td>
<td>any</td>
<td>any</td>
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<tr>
<td>High Risk</td>
<td>2a/2b</td>
<td>any</td>
<td>amp</td>
<td>any</td>
<td>any</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>3</td>
<td>&lt;547d</td>
<td>not amp</td>
<td>any</td>
<td>FH</td>
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<td>Intermediate Risk</td>
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<td>UH</td>
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<tr>
<td>High Risk</td>
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<td>&lt;365d</td>
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<td>365-&lt;547d</td>
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<td>any</td>
<td>any</td>
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<tr>
<td>High Risk</td>
<td>4</td>
<td>365-&lt;547d</td>
<td>any</td>
<td>Dl=1</td>
<td>any</td>
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<tr>
<td>Intermediate Risk</td>
<td>4</td>
<td>365-&lt;547d</td>
<td>not amp</td>
<td>any</td>
<td>FH</td>
</tr>
<tr>
<td>High Risk</td>
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<td>amp</td>
<td>any</td>
<td>any</td>
</tr>
</tbody>
</table>
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
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
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

**Surgery**

**PBSC (BM) Harvest**

**PBSC Infusion**

**SCT**

**XRT**

**RA + Anti-GD2 Ab and cytokines**
The Children’s Oncology Group unites more than 9,000 experts in over 200 children’s hospitals, universities and cancer centers, into a global team dedicated to the cure of all children with cancer.

Learn More
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%)
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.
Neuroblastoma – ANBL1531

**On Study**

- **Cycle 1 (TOPO/CPM), ALK screening, and central MIBG review**

**Randomized**

- Arm A
- Arm B
- Arm C (ASSIGNED)

**Assigned**

- Arm D
- Arm E

**All Others**

**Primary tumor response evaluation**: Patients with progressive disease will go off protocol therapy

**Cycle 2 (TOPO/CPM)**

**PBSC Harvest**

- Cycle 3 (CDDP/ETOP)
- Cycle 4 (VCR/DOXO/CPM)

**MIBG Non-Avid without ALK Aberration**

- Arm E

**Arm A**

**POST-CONSOLIDATION THERAPY**: Dinutuximab + GM-CSF and isotretinoin

**Arm B**

**CONSOLIDATION THERAPY**: Dinutuximab + GM-CSF and isotretinoin

**Arm C**

**CONSOLIDATION MIBG**

**Arm D**

**HSCT #1 (TC)**

**HSCT #2 (CEM)**

**Local XRT**

**Arm E**

**Cycle 2 (TOPO/CPM + CRIZ)**

**Cycle 3 (CDDP/ETOP + CRIZ)**

**Cycle 4 (VCR/DOXO/CPM + CRIZ)**

**Primary tumor response evaluation**: Patients with progressive disease will go off protocol therapy

**Surgery**

- Cycle 5 (CDDP/ETOP)

**Full response evaluation**: Patients with progressive disease will go off protocol therapy

- HSCT #1 (TC)
- HSCT (BuMel)

- HSCT #2 (CEM)
- HSCT #2 (CEM)

- Local XRT + CRIZ

**HSCT #1 (TC)**

**HSCT #2 (CEM)**

**Local XRT**

**CRIZ post recovery**

**CONTINUATION THERAPY (CRIZ)**

**POST-CONSOLIDATION THERAPY**: Dinutuximab + GM-CSF and isotretinoin
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

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>Immunotherapy (N=137)</th>
<th>Standard Therapy (N=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurpathic Pain</td>
<td>71 (52)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>24 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>18 (13)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fever without neutropenia</td>
<td>53 (39)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Acute Capillary Leak</td>
<td>31 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity Reaction</td>
<td>34 (24)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>18 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Infection (any)</td>
<td>54 (39)</td>
<td>24 (22)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (13)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>31 (23)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>48 (35)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Abnormal ALT</td>
<td>31 (23)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Abnormal AST</td>
<td>14 (10)</td>
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</tr>
<tr>
<td>Hypercalcemia</td>
<td>7 (5)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Ocular Symptoms</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Side Effects

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</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>50 (37)</td>
<td>30 (24)</td>
<td>23 (19)</td>
<td>33 (29)</td>
<td>15 (14)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hypersensitivity Reactions</td>
<td>14 (10)</td>
<td>33 (26)</td>
<td>6 (5)</td>
<td>29 (25)</td>
<td>13 (12)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Capillary Leak Syndrome</td>
<td>9 (7)</td>
<td>14 (11)</td>
<td>8 (7)</td>
<td>15 (13)</td>
<td>3 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

• 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\(^1,2\)

### Side Effects


<table>
<thead>
<tr>
<th>First Author</th>
<th>Therapy</th>
<th>Tumor Type and No. of Patients</th>
<th>Toxicity</th>
<th>Pharmacology</th>
<th>HACA Positivity (no. of patients)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saleh</td>
<td>Phase I ch14.18 only</td>
<td>13 with metastatic melanoma</td>
<td>Neuropathic pain</td>
<td>T1/2a 24 ± 1 hour, T1/2b 181 ± 73 hours</td>
<td>8/13</td>
<td>No response</td>
</tr>
<tr>
<td>Handgretinger</td>
<td>Phase I ch14.18 only</td>
<td>9 with stage IV neuroblastoma</td>
<td>Neuropathic pain, pruritus, urticaria, transient pupillodilatation</td>
<td>Not done</td>
<td>0/9</td>
<td>2 CRs, 2 PRs, 1 minor response</td>
</tr>
<tr>
<td>Yu</td>
<td>Phase I ch14.18 only</td>
<td>10 with refractory neuroblastoma and 1 with osteosarcoma</td>
<td>Neuropathic pain, tachycardia, hypertension, fever, urticaria</td>
<td>CDC activity against neuroblastoma cells in 5/5 patients</td>
<td>3/8</td>
<td>1 PR, 4 mixed responses</td>
</tr>
<tr>
<td>Murray</td>
<td>Phase I ch14.18 + GM-CSF</td>
<td>16 with metastatic melanoma</td>
<td>Neuropathic pain, hypertension, hypotension, headache, nausea, diarrhea, peripheral nerve dysesthesias, myalgias, weakness</td>
<td>T1/2b 123 ± 29 hours; increased ADCC activity in 10/11 patients</td>
<td>6/16</td>
<td>No response</td>
</tr>
<tr>
<td>Yu</td>
<td>Pilot ch14.18 + GM-CSF</td>
<td>17 with refractory neuroblastoma</td>
<td>Neuropathic pain, fever, tachycardia, hypertension, nausea, vomiting, diarrhea, hypotension, hypokalemia, urticaria, transient thromboocytopenia</td>
<td>Increased ADCC activity in 5/9 patients</td>
<td>Not done</td>
<td>3 CRs, 1 PR, 2 mixed responses</td>
</tr>
<tr>
<td>Yu</td>
<td>Phase II ch14.18 + GM-CSF</td>
<td>32 with refractory neuroblastoma</td>
<td>Neuropathic pain, fever, tachycardia, hypertension, nausea, vomiting, diarrhea, hypotension, hypokalemia, urticaria, transient thromboocytopenia</td>
<td>All responding patients had increased ADCC</td>
<td>Not reported</td>
<td>Among 27 available for response: 1 CR, 3 PRs, 1 mixed response</td>
</tr>
<tr>
<td>Ozkaynak (current study)</td>
<td>Phase I ch14.18 + GM-CSF immediately post-HSCT</td>
<td>19 with neuroblastoma</td>
<td>Neuropathic pain, fever, nausea, vomiting, urticaria, hypotension, capillary leak syndrome, dilated pupils, diplopia, transient thromboocytopenia</td>
<td>Mean peak ch14.18 level 5.607 ng/mL at 40 mg/m²/d (MID)</td>
<td>5/18</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
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 deterioration, 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
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
  – Treatment: gabapentin, narcotic infusions
  – Collaboration with APMS
Dinutuximab and Pain

• Specific binding of Dinutuximab to neurons & peripheral nerve fibers which express GD2\textsuperscript{1,2,3,4}

  • Pain of grade 3 or 4 was observed in 52% of patients\textsuperscript{1}
    – Ranging from 33-87%
    – Major toxicity was neuropathic pain\textsuperscript{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 similarly to neuropathic pain syndromes, however transient and persists duration of ch 14.18 infusion\textsuperscript{7}

• Common site of pain presentation: abdomen > extremity
Dinutuximab and Pain Management

• Use of opioids for the duration of antibody therapy is essential\textsuperscript{2,4}

  – Child Oncology Protocol\textsuperscript{7} - Loading dose 50 mcg/kg, infusion 20-50 mcg/kg/hr

  – Phase I studies\textsuperscript{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\textsuperscript{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 \textsuperscript{2,3}
<table>
<thead>
<tr>
<th>Study</th>
<th>Analgesic Modality</th>
<th>Total Analgesic Consumption</th>
<th>Side Effects Related to Analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozkaynak 8</td>
<td>Morphine 0.1 mg/kg bolus + 0.05 mg/kg/hr</td>
<td>Not listed</td>
<td>Listed for dinutuximab but not isolated for opioid</td>
</tr>
<tr>
<td>Wallace</td>
<td>Lidocaine 2 mg/kg + 1 mg/kg/hr OR Morphine 0.1 mg/kg + 0.05-0.1 mg/kg/hr OR Morphine 0.05 mg/kg q 2 hrs PRN</td>
<td>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</td>
<td>No significant change in BP Increased HR Increased emesis day 4 – LIDO</td>
</tr>
<tr>
<td>Gorges</td>
<td>Hydromorphone 2 - 8 mcg/kg/hr  OR Dexmedetomidine 0.1-0.6 mcg/kg/hr +/- Gabapentin</td>
<td>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</td>
<td>Percentage of treatment days Hypotension – 30 Hypoxemia – 8 Bradycardia - 4</td>
</tr>
<tr>
<td>Ari 7</td>
<td>NCA/PCA Morphine demand dose 0.02-0.04 mg/kg lockout 8 – 20 minutes + basal 0.02-0.04 mg/kg/kd/hr</td>
<td>Mean total daily morphine 0.46 mg/kg/d = 460 mcg/kg/day (mean daily amounts 0.448, 0.396, 0.335, 0.335 mcg/kg/day on days 1-4 respectively)</td>
<td>No reports of respiratory depression or life-threatening events Hypotension and tachycardia 37%</td>
</tr>
<tr>
<td>Bertolizio 9</td>
<td>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 4 hrs PRN</td>
<td>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</td>
<td>Incidence of desaturations 4.2% - no episodes &lt;90 or respiratory arrest Hypotension 2.3% in cycle 1 to 0.3% in cycle 3 No hallucinations/tachycardia</td>
</tr>
</tbody>
</table>
Opioids

• Case series 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

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

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

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 min PRN + 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

Ketamine

• Results

• Mean Pain Scores ranged between 0.3-0.6

• Highest daily median morphine consumption 0.29 mg/kg/day in cycle 3

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

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-GD2 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-GD2 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.
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 continuous 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 continuous opioid infusion for 4 day cycle and stop 1-2 hrs following Dinutuximab
**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)
KHSC Dinutuximab Protocol Overview

1. Pediatric Anesthesia Consult 2-3 weeks prior
2. Oncology will notify APMS prior to patient’s admission
3. Patient admitted to PCCU evening prior to start of infusion
4. APMS consultant suggest/MRP for pain management
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*)
### 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 8h.
- 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/m²/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 10⁹/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
References

QUESTIONS