Nuclear Medicine Therapy in Pediatric Oncology

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• Brief overview pediatric thyroid cancer epidemiology and radioiodine therapy

• Background and current status of $^{131}$I-MIBG therapy in neuroblastoma

• Understanding the logistic and radiation considerations of $^{131}$I-MIBG therapy program

• Newer radionuclide therapies/future directions
• Thyroid cancer is a rare malignancy of childhood and among all cancers it accounts for 0.7%

  – Differentiated thyroid cancer (DTC, both papillary and follicular) comprises 90-95% of all childhood thyroid cancers
  – medullary thyroid cancer 5-8%,
  – undifferentiated tumors extremely rare
• Compared with adults, children with DTC present with more advanced stage disease and higher recurrence rates
  – Lymph node involvement at diagnosis in 40–90% of children vs. 20–50% of adults
  – Prevalence of distant metastases, 20 –30% in children vs. 2% in adults
  – Multifocal disease is more common in children, about 40% of childhood papillary thyroid cancer cases

Endocrine Reviews 32: 798–826, 2011
• Total thyroidectomy + central compartment lymph node dissection + radioactive iodine reduce recurrence rate

• Routine ablation of thyroid remnants in children with single focus microcarcinomas with no nodal metastases recommended (~30mCi, may need a second dose) vs. optional in adults

• To facilitate $^{131}$I uptake by remnant tissue or residual tumor, thyroid hormone withdrawal is used (TSH>30mU/L). Recombinant TSH use is not approved for children
• Radioiodine therapy (empiric activity selection)
  – 100–150 mCi for thyroid bed disease,
  – 150 mCi when cervical nodes involved,
  – 200 mCi for lung metastases. Activities adjusted for body size

Endocrine Reviews 32: 798–826, 2011
Thyroid 20:1095–1101

• Blood-dose limiting-based or lesion-based dosimetry should be considered for children with metastatic disease to the lungs and other sites

• Outpatient vs. inpatient. Long term follow up. Radiation risks
Diagnostic WB $^{123}$I scintigraphy

- Dose ~3mCi, WB sweep, static imaging of head/neck/chest
- Medium energy collimator
- Physiologic sites of uptake
Post $^{131}$I radioiodine therapy scans

- Thyroid remnant/thyroid bed disease
- Thyroid remnant/thyroid bed disease + nodal mets
- Thyroid remnant/thyroid bed disease + nodal + lung mets
• Neuroblastoma is the most common extracranial solid tumor in children (~30% of infantile cancers). Median age at diagnosis 15 months

• Most common sites of origin
  – Adrenals (48%)
  – Extra-adrenal retroperitoneum (25%)
  – Chest (16%)

• Approximately 60% patient with metastases (bone marrow or cortical bone, lymph nodes and liver)
# Staging system

<table>
<thead>
<tr>
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<th>International Neuroblastoma Staging System (INSS)</th>
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| 1 | Localized tumor with complete gross resection  
No regional lymph node involvement |
| 2 | Localized tumor with incomplete gross resection or Ipsilateral lymph node involvement |
| 3 | Tumor crossing midline or Contralateral lymph node involvement |
| 4 | Tumor with distant metastases |
| 4s | Patient <12 months with localized tumor and metastases confined to liver, skin and/or marrow |
• The Children’s Oncology Group (COG) uses major prognostic factors including age, histology and molecular pathology in combination with INSS stage of the disease, to place children into 3 risk groups

• Poor prognostic features
  – Age >18 months
  – N-MYC gene amplification
  – Diploid DNA content
  – Poorly differentiated/undifferentiated tumor histology
• **Low-risk disease** with survival rate of 90% with surgery, spontaneous regression or maturation of disease without treatment

• **Intermediate-risk disease** with survival rate of 90% with surgery and chemotherapy

• **High-risk** neuroblastoma with survival rate of ~30%
### COG risk groups

<table>
<thead>
<tr>
<th>INSS Stage</th>
<th>N-myc NON-amplified</th>
<th>N-myc Amplified</th>
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<tr>
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<td>Age &lt; 18 mo</td>
<td>Age &gt; 18 mo</td>
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<tr>
<td>1</td>
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<td>Low Risk</td>
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<td>2</td>
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<td>3</td>
<td>Intermediate Risk</td>
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Background and current status

- High MIBG avidity and known radiosensitivity of neuroblastoma makes $^{131}$I-MIBG a potential therapeutic agent. Neuroblastoma cells take up MIBG via specific active uptake by the norepinephrine transporters.

- $^{131}$I-MIBG currently not FDA approved. Investigational drug for treatment of both relapsed and newly diagnosed cases in clinical trials (phase 1 and phase 2 studies).

- Expanded access protocol of FDA.
• Early clinical trials of $^{131}$I-MIBG defined toxicity profile. Myelosuppression main dose-limiting toxicity

• Subsequent trials showed $^{131}$I-MIBG to be active against refractory neuroblastoma and superior to almost every other novel agent in the setting of relapsed high-risk disease

• Response rates of 20-40% in patients with relapsed or refractory disease. Controls tumor growth and pain relief

• Several studies suggested a dose-related response. Dose escalation studies demonstrated tolerability of sequential high doses of $^{131}$I-MIBG with stem cell rescue

• Studies support use of no-carrier-added $^{131}$I-MIBG. Lower risk of chemical pharmacologic adverse effects and the ability for more rapid infusion

• Most clinical benefit with $^{131}$I-MIBG therapy occurs after the first cycle of therapy, although additional responses may be observed with subsequent cycles
• More recent studies have focused on use of $^{131}$I-MIBG in combination with chemotherapy or myeloablative regimens

• $^{131}$I-MIBG is also now being investigating for incorporation into the initial therapy for newly diagnosed high-risk neuroblastoma patients by the COG and others (European studies)

• About 9 North American and at least 7 European pediatric centers regularly administer MIBG therapy, more centers in development
131I MIBG therapy program planning

• A multidisciplinary approach
  – Pediatric oncologists and nurses, family caregivers, nuclear medicine team, radiation safety

• Only medically stable patients are selected. Inpatient admission

• Dose (5-18 mCi/kg) at investigator's discretion

• Any dose ≥12 mCi/kg requires stored stem cells

• Agent diluted in normal saline and infused intravenously over 90-120 minutes

• ECG monitoring and automated blood pressure measurement during infusion

• After completion of infusion, older patients are encouraged to void frequently, younger patients catheterized

• Whole body Imaging is obtained prior to patient discharge. Typically 3-5 days post infusion

• Static images for 300,000-500,000 counts. High-energy collimator used

Four-year-old girl with stage 4 high-risk neuroblastoma following 131I-MIBG therapy

Planar images four days after treatment with 309.2 mCi of 131I-MIBG show extensive MIBG-avid disease in the chest and abdomen
• All caregivers, including nursing staff, receive radiation doses well below those allowed under current regulations for individuals exposed to therapy patients (<5.0 mSv)

• Sharing patient care among nurses and family caregivers is a safe and feasible treatment model to minimize radiation exposure
Toxicity/side effects

- Hematologic toxicity (notably thrombocytopenia) is the most common and serious side effect.

- Myelosuppression occurs within 2-4 weeks after therapy. The nadir is observed typically after 4-6 weeks.

- Most common early side effects are:
  - blood pressure changes (during infusion)
  - nausea and vomiting (48 h)
Peptide receptor radionuclide therapy

• Somatostatin receptor expression in several embryonal tumors in children, including >90% of neuroblastoma and medulloblastomas and ~35% of Ewing’s sarcomas

• Development of somatostatin analogs labeled with beta-emitting radionuclides for peptide receptor radionuclide therapy of neuroendocrine tumors. Most common radiopharmaceuticals are $^{90}$Y-DOTA$^{0}$-Tyr$^{3}$-octreotide (DOTATOC) and $^{177}$Lutetium-DOTA$^{0}$-Tyr$^{3}$-Thre$^{8}$-octreotide (DOTATATE)
• Therapy with $^{90}$Y-DOTATOC octreotide demonstrated a favorable safety profile in a phase 1 study in children and young adults (N=17) with refractory solid tumors that express somatostatin receptors. No dose limiting toxicities were observed. Dose limiting factor renal radiation exposure


• Treatment with $^{177}$Lu-DOTATATE was feasible, practical, and well tolerated in a small group of patients (N=8) with high-risk neuroblastoma

Palliative bone seeking radionuclide therapies

- In palliative situations bone seeking radionuclide therapies (strontium-89, Samarium-153) may be offered to patients with painful metastatic osteosarcoma or in case of recurrent bone sites inaccessible to local therapies


- A phase 1/2 clinical trial is currently recruiting patients at MD Anderson, Texas (NCT01833520) to find the maximum tolerated Dose of Ra-223 Dichloride in progressive, locally recurrent, or metastatic Osteosarcoma

  https://clinicaltrials.gov/ct2/show/record/NCT01833520
Dosimetry

- Some groups have utilized dosimetry either from a tracer MIBG dose or from an initial therapeutic MIBG dose in order to
  - prescribe a $^{131}$I-MIBG activity calculated to produce a given whole-body radiation dose
  - estimate tumor-specific radiation dose that may correlate with treatment response
  - determine organ-specific doses

- $^{131}$I-MIBG not ideal for imaging for dosimetry
Recent preclinical studies in mice neuroblastoma models demonstrate feasibility of $^{124}$I-MIBG PET/CT dosimetry. Similar biodistribution and half life to $^{131}$I, more accurate quantification, lower radiation dose

Med Phys. 2010 Sep;37(9):4861-7

Results from an ongoing pilot study (clinical trial NCT01583842) of $^{124}$I-MIBG pretherapy PET/CT imaging for patients undergoing $^{131}$I-MIBG therapy could clarify the use of $^{124}$I-MIBG PET/CT dosimetry in human subjects

Theranostics and personalized nuclear medicine
• Radioiodine therapy plays an important role in reducing risk of recurrence and mortality in children with DTC

• $^{131}$I-MIBG is active against refractory neuroblastoma and superior to almost every other novel agent studied in the setting of relapsed high-risk disease with response rates of 20-40%

• The role of newer radiopharmaceuticals in children, such as $^{177}$Lu-DOTATATE targeting the somatostatin receptor and newer bone seeking radionuclide therapies ($^{223}$Ra) still needs to be defined