Targeted Radiotherapy for Refractory Neuroblastoma

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Neuroblastoma

- Malignancy of postganglionic sympathetic nervous system
  - Persistence of embryonic progenitor cells give rise to neuroblastic tumor cells
- Most common solid tumor in children
- Diverse clinical/biological behavior
  - Spontaneous regression vs. extremely malignant and widely disseminated disease
- Genetic predisposition
  - *PHOX2B*, *MYCN* mutations
Clinical Presentation

- Commonly begins in adrenal gland, nerve tissues of neck, chest, abdomen, or pelvis
- 50% of patients present with metastasis
  - Patients after one year of age have a 70% chance of exhibiting metastatic disease at the time of diagnosis
  - Usually very ill-appearing at presentation
Diagnosis and Staging

- Risk stratification (INSS)
- Relapse patients have < 10% survival
- Currently no standard therapies for relapsed or refractory neuroblastoma patients (high risk)

*Figure 4: Survival of patients with neuroblastoma based on risk group*

Patients treated between 1986 and 2001 in Children’s Cancer Group, Pediatric Oncology Group, and Children’s Oncology Group studies were classified as low-risk, intermediate-risk, and high-risk at diagnosis based on clinical and biological features. Kaplan-Meier survival analysis shows marked differences in event-free survival for these groups of patients. Data courtesy of W London, Children’s Oncology Group statistical office.
MIBG Background

- Meta-iodobenzylguanidine
  - Norepinephrine analog that concentrates selectively in sympathetic nervous system in more than 90% of neuroblastomas
  - Radioactive iodine ($^{131}$I or $^{123}$I) combined with MIBG for diagnosis
    - At higher doses, used for therapy

Image courtesy of Maris et. al
MIBG Therapy

- Pilot studies in 1980’s and 1990’s using low doses established activity in palliative setting (Hutchinson, JNM 1991; Kang, JPHO 2003; etc.)

- Phase I trial established feasibility of dose intensification (Matthay, JCO 1998)

- Pilot trials combining MIBG with chemotherapy in US and Europe
131I-MIBG Phase II Study

- Phase II trial (2007)
  - Aims:
    - Response rate to 18 mCi/kg 131I-MIBG
    - Acute and late toxicities
  - Treatment: 2 hour MIBG infusion + in-patient stay
  - Response evaluation at 6 weeks
131I-MIBG Phase II Study Conclusions

- 131I-MIBG is a safe radiotherapeutic in heavily pretreated patients with refractory neuroblastoma
  - Peripheral blood stem cell support allows dose intensification
- 131I-MIBG is active against refractory neuroblastoma
  - Response rates in patients with relapse after HSCT 35-55% regardless of site
  - SD/NR often accompanied with clinical benefit
Toxicity

- Hematologic toxicity universal
  - 65% with ANC <200
  - 88% required platelet transfusion
  - 33% treated with 18 mCi/kg required PBSC support
- Non-hematologic toxicity minimal
Low-dose MIBG therapy

Primary Aim:

- Determine the response rate to low-dose (1.0-2.5 mCi/kg) repetitive $^{131}$I-MIBG treatment for patients with refractory neuroblastoma.

Secondary Aim:

- Determine the acute and long-term toxicity of low-dose repetitive $^{131}$I-MIBG treatment for patients with refractory neuroblastoma.

- Retrospectively compare response rate and toxicities to those obtained with high-dose MIBG therapy.
Low-dose MIBG therapy

- Eligibility criteria
  - Diagnosis: refractory or relapsed neuroblastoma
  - Age > 1 year
  - Disease status: failure to respond to standard therapy or development of progressive disease; disease evaluable by MIBG scan within 8 weeks of study entry
  - Prior therapy: patients must have fully recovered from prior therapy and at least 2 weeks should have elapsed since any anti-tumor activity
  - Organ function within specified limits
Low-dose MIBG therapy

- Similar protocol to Phase II Trial (2007)
- Observations involve
  - Physical exam
  - Complete blood count labs
  - Liver function tests
  - Thyroid function tests
  - Urine catecholamines
  - Tumor imaging
- Protocol pending approval
Ongoing Clinical Trials

- **MIBG Trials**
  - NANT 99-01 (MIBG/CEM/SCR Phase I)
  - NANT 01-02 (MIBG/CEM/PBSCR)
  - NANT 01-03 (CEP)
  - NANT 04-06 (Irino/VCR/MIBG)
  - **NANT 07-01 (Ultratrace MIBG)**
  - CHOP 830 (MIBG Phase II): Compassionate Use

- **Other therapies**
  - ABT 751: oral tubulin-binding agent
  - Immunotherapy
  - Tyrosine kinase inhibitors
  - Various cytotoxic agents
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