The Path to Survivorship in Pediatric Cancers

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Disclosures, conflicts of interest

• I have nothing to disclose
Learning objectives

• Contextualize radiation therapy into the bigger picture of treatment for several childhood cancers
• Understand the evolution of cancer therapy in pediatric cancers
• Recognize the health related and psychosocial struggles faced by childhood cancer survivors
Presentation outline

• Background
• 3 cases/3 representative cancers
• Treatment, late effects, newer therapeutics, future directions
• Late effects in general and importance of survivorship
Pediatric cancer: scope of the problem

• In 2014, there were 15,780 new cancer diagnoses in children ages 0-19
• 1/285 children will be diagnosed with cancer before the age of 20 (0.35%)
• Leading cause of disease related death in children

American Cancer Society: Cancer Facts and Figures 2014
Incidence of cancers by subtype in children ages 0-19

- Acute Lymphoblastic Leukemia (ALL): 20%
- Brain and Central Nervous System: 18%
- Hodgkin Disease: 8%
- Non-Hodgkin Lymphoma: 7%
- Acute Myeloid Leukemia (AML): 5%
- Neuroblastoma: 5%
- Bone Tumors*: 5%
- Thyroid Carcinoma: 4%
- Wilms / Kidney: 3%
- Germ Cell Tumors: 3%
- Rhabdomyosarcoma: 2%
- Retinoblastoma: 2%
- Melanoma: 2%
- Other: 16%

American Cancer Society: Cancer Facts and Figures 2014
Success story of modern medicine
The world's childhood cancer experts

The Children's Oncology Group and its predecessor organizations have had a pivotal role in transforming childhood cancer from a virtually incurable disease 50 years ago to one with a combined 5-year survival rate of 80% today.

Learn More

For Patients and Families

The Children's Oncology Group provides important information for children and their families from the time of diagnosis, through treatment and following cure. Our experts in childhood cancer are available throughout the United States, Canada and a number of international sites. Find a Children's Oncology Group location near you and download our Patient Handbook for more information.

Project:EveryChild

Children's Oncology Group's Project:EveryChild is our ambitious initiative to find better cures for every type of childhood cancer, no matter how rare. All children with cancer cared for at COG's more than 200 pediatric cancer programs will be able to participate in Project:EveryChild. Learn more about Project:EveryChild, including our Hyundai Hope On Wheels Research Program and how you can help.

Supporting Us

The Children's Oncology Group is dedicated to improving the outcome for all children with cancer. Our global research team needs your help to turn today's discoveries into tomorrow's cures. With more than 90% of children with cancer cared for at COG sites, learn how you can help be part of the cure.
Modalities to treat childhood cancer

1970s - Surgery, Radiation, Chemotherapy
1980s - Chemotherapy Combinations
1990s - Targeted Therapy
2000s - Targeted Therapy Plus Chemotherapy
Present - Next-Generation Targeted Therapy, Immunotherapy

Google images: thelungcancerproject.org
The challenge of treating childhood cancers: cost of cure

**Cure**
- Still the leading cause of disease related death in children > 12 months
- ~1,190 children are expected to die from the disease in 2017

**Survivorship**
- In 2013, there were ~ 408,283 childhood cancer survivors in US
- Unique health related and psychosocial challenges faced by survivors
Case 1: patient EC

- 4 yo M with fatigue, bruising, petechiae, leg pain, found to be pancytopenic
- BMA/Bx revealed hypercellular marrow with 70% involvement by B cell ALL CNS 1
- NCI SR – 3 drug induction
- Day 29 MRD positive -> HR risk B ALL, treated with augmented therapy
- Received prophylactic cranial radiation 1200 cGy

Google images: dontforgethebubbles.com/acute-lymphoblastic-leukemia-2/
B cell lymphoblastic leukemia

- Most common childhood cancer – 4000 *de novo* cases diagnosed each year in US
- Risk stratified therapy delivers appropriately intense chemotherapy to subgroups of disease
- Response to induction therapy is predictive of relapse- occurs in 15-20% of cases and associated with high mortality
Treatment of acute lymphoblastic leukemia

Induction 28 days
- Prednisone
- Vincristine
- PEG Asparaginase
- Daunorubicin
- Intrathecal Methotrexate

Consolidation 28-56 days
- Cyclophosphamide
- Cytarabine
- Mercaptopurine
- Vincristine
- IT Methotrexate
- PEG Asparaginase
- *testicular radiation
- *cranial radiation (CNS3)

Interim Maintenance 1 63 days
- Vincristine
- IV Methotrexate
- PEG Asparaginase
- IT Methotrexate

Delayed Intensification 56 days
- Vincristine
- Dexamethasone
- Doxorubicin
- Cyclophosphamide
- Cytarabine
- Thioguanine
- IT Methotrexate
- *cranial radiation (CNS3)

Interim Maintenance 2 56 days
- Vincristine
- IV Methotrexate
- IT Methotrexate

Maintenance
- Vincristine
- IT Methotrexate
- Steroid
- Mercaptopurine
- PO Methotrexate
- *cranial radiation (CNS3)
Cranial irradiation in ALL

- Systemic therapies (HD Methotrexate, Dexamethasone, IT therapy) has been able to sufficiently decrease CNS relapse in all groups except CNS3 and T cell subsets (CNS3 = > 5 blast/HPF)

- B cell ALL – cranial irradiation has been eliminated for all subgroups except CNS3 – therapeutic (1800 cGy)

- T cell ALL – prophylactic (1200 cGy) for VHR CNS1 CNS2 and therapeutic (1800 cGy) for CNS3

RT given in 2% of B cell patients
Radiation related neuro-cognitive sequelae

- Radiotherapy causes white and gray matter changes including inflammation, angiogenesis and cell death
- Age, cumulative dose, and brain volume
- Children < 5 experience the greatest decline in cognition
- The risk of > 10% decline in full-scale IQ is significantly higher in children < 15

EC Late effects of therapy

- Below average functioning in visual, verbal, working memory, processing speed, attention, cognitive flexibility, expressive language and verbal fluency, and verbal reasoning (neuropsychiatric testing) – IEP in place
- At risk for eye disease (glaucoma and cataracts)
- At risk for cardiovascular disease (lifelong screening)
- At risk for osteopenia/osteoporosis (Dexa scan at puberty, Vit D supplementation)
- At risk for dental disease
- At risk for pituitary dysfunction (including growth restriction), hearing loss
- At risk for secondary malignancies (primarily brain tumors and myeloid leukemia, CBCs yearly until 10 years off therapy)
Patient EC Relapse

- Age 8, 16 mo off therapy (>36 mo after CR1) petechiae, bruising and thrombocytopenia
- Bone marrow demonstrated relapse of pre B ALL, same immunophenotype
Management of relapsed ALL

• “Risk” of relapse
  • Duration of remission (early < 18 mo, intermediate 18-36 mo, late > 36 mo)
  • Site of relapse (marrow, CNS, testicles)
  • Initial risk of disease
• Cure rates range from 20-50% based on risk
• Chemotherapy
• Chemoradiotherapy
• Allogeneic stem cell transplant
• Immunotherapy (antibody based and/or adoptive cellular therapy)
Setting the Body’s ‘Serial Killers’ Loose on Cancer

After a long, intense pursuit, researchers are close to bringing to market a daring new treatment: cell therapy that turbocharges the immune system to fight cancer.

By ANDREW POLLACK  AUG. 1, 2016.
Encouraging results

- Feasible and safe
- Side effects are now well defined
- Up to 90% CR in heavily pre-treated refractory population
- Sustained response demonstrated up to 2 years
- Penetration of CSF demonstrated
- Phase 2 studies to determine efficacy are underway

Clinical sequelae of CAR T cell therapy

Future of CAR T cell therapy

- For which patients and at what disease status should CAR T cell therapy be utilized?
- What is the role of CAR T cell therapy (definitive therapy vs bridge to HCST)?
- Is CAR T cell persistence long term necessary for ongoing remission?
- What are the long term effects of CAR T cell therapy?
- Expansion to other malignancies.
Patient EC update

• Underwent infusion of autologous CAR T cells at OHSU enrolled on phase 2 Novartis 2205J CTL019 study
• Day 7 developed mild CRS with fever only
• Day 29 workup demonstrated ALL in remission and persistence of CAR T cells
• Day 100 workup demonstrated ALL in remission but return of circulating CD19 B lymphocytes and absent CAR T cells
• Recommending autologous SCT
Case 2: patient JC

- 5 yo with abdominal pain, constipation, gait changes and fatigue.
- Anemic with Hgb 9.8 gm/dl
- Urine HVA/VMA elevated
  Diagnosis made via MA/Bx
Staging workup

• Multiple bony metastases and bone marrow involvement – Stage 4 disease

• Pathology demonstrated n-myc amplification

  High risk disease
Neuroblastoma

- Most common malignancy in infants
- Most common extra cranial solid tumor of childhood
- Third most common cancer in children
- Average age at diagnosis is 17 months
- 50-60% are metastatic or HR at presentation

Google images:steadyhealth.com/articles/a-parents-guide-to-understanding-neuroblastoma
Treatment progress in HR neuroblastoma

- Prior to late 1990s/early 2000s, long term survival ~ 20%
- Backbone therapy involves intensive chemotherapy blocks, surgery, and consolidation with autologous stem cell transplant and radiation
- cis-RA was found to cause maturation in neuroblastoma cell lines

Matthay, K et al. NEJM. 1999; 341: 1165-1173
Immunotherapy in neuroblastoma
Treatment progress in HR neuroblastoma

Yu, AL, et al. NEJM. 2010; 363(14) 1324-1334
Current therapy for HR Neuroblastoma

**Induction**
- Cycles 1, 2: CPM + Topo
- PBSC Harvest
- Cycles 3, 5*: CDDP + Etop
- Cycles 4, 6 CPM + Doxo + VCR
- *surgical resection after cycle 5

**Consolidation**
- Double tandem ASCT
- Radiation therapy*
- *pre-surgical primary tumor volume and metastatic sites after induction

**Maintenance**
- Immunotherapy with Anti-GD2 MoAbCh14.18 (Dinutuximab) + cytokines + isotretinoin x 6 cycles
Late effects of HR neuroblastoma therapy

- Secondary malignancies (myeloid malignancy, MDS, thyroid cancers) 18 fold increase
- Infertility (Carbolatin)
- Hearing loss (Cisplatin and Carboplatin)
- Cardiotoxicity (Doxorubicin)
- Hepatotoxicity (VOD) - fibrosis
Future directions of neuroblastoma therapy

- MIBG – I-131 therapy – up front?
- Alk inhibition – up front for mutated tumors
- CAR T cell immunotherapy
- DFMO therapy in maintenance?

Barone, G et al CCR New Strat. 2013; 10. 1158/1078-0432
Update patient JC:

- Poor response to induction chemotherapy requiring additional cycle of chemotherapy with up front anti-GD2 (Unituxin) therapy
- Developed eye pain and vision loss acutely with anti-GD2 infusion requiring cessation
- Underwent surgery, 2 consolidative ASCT cycles and radiation
- Attempted first cycle of immunotherapy with Dinutuximab – again had vision loss so immunotherapy discontinued
- Will complete 12 weeks of cis-RA and enroll on study to receive DFMO for maintenance ~ 2 years
Case 3: patient TN

- 3 yo Vietnamese boy presented with 2 year history of progressive left sided weakness, early right hand preference and late developmental milestones.
Surgery

- Sub-total resection ~ 80%
  - Tumor invading the brain stem, amygdala, hypothalamas
- Pathology revealed pilocytic astrocytoma (WHO grade I) with pilomyxoid features (WHO grade II) Low Grade Glioma

Photo credit: Dr. Deborah Shuster Neuro-pathology
Pediatric Low Grade Glioma (PLGG)

- Largest subgroup of pediatric CNS tumors – 40-45%
- Peak incidence in first decade of life
- Unlike adult LGG, rarely associated with malignant transformation – histologically benign (low proliferative potential)
- JPA commonly occurs in posterior fossa (80%) and other midline locations (optic pathway, hypothalamus, basal ganglia, and brainstem).
- Pilomyxoid astrocytomas occur mainly in the hypothalamus-chiasmatic region
- Widespread CNS dissemination occurs in ~5% of patients
Management of PLGG

Management of progressive/recurrent disease

- Historically radiation was the standard of care for progressive disease
- Survival rates in children with supratentorial LGG treated with radiation 40-70% at 5 years and 11-50% at 10 year
- Midline supratentorial location occurs more commonly in young children who are more susceptible to radiation neurocognitive sequelae
Chemotherapy

• Various chemotherapy regimens have demonstrated efficacy in achieving partial response
  • 6-TG, Lomustine, Procarbazine, Vincristine – 58% RR and 34% EFS at 5 years
  • Carboplatin and Vincristine – 57% RR and 48% EFS at 5 years
  • Vincristine and Dactinomycin – 62% PFS
  • Temozolamide – 49% PFS at 2 years

Median time to progression 3-5 years
Treatment of recurrent PLGG

• Multiple courses of different chemotherapy regimens
• Prolonged periods of stable tumor are considered “treatment response”
• Role in delaying radiation
• Need for new therapies
Targeting angiogenesis

• Gliomas are hyper-vascular and routinely overexpress pro-angiogenic factors VEGF, EGF, PDGF, FGF, SDF-1, Tie2, and TGF-beta.

• Bevacizumab (Avastin) – anti-VEGF monoclonal Ab FDA approval for recurrent glioblastoma in adults

• In children with recurrent LGG, Bevacizumab has shown ORR 70% by imaging and symptom improvement with PFS 85% at 6 mo and 47% at 5 year

• TKI Sunitinib and Sorafenib target VEGF
Molecular therapeutic targeting

- A fusion oncogene, *KIAA1549:BRAF*, leads to MAPK and MEK dependent mTOR activation and is present in 65-75% PLGG

- A point mutation, *BRAF V600E* (valine to glutamate substitution), leads to MAPK activation and is present in 5-10% of PLGG

- mTOR activation is present in 50% LGG

  TOR activation is associated with NF1
BRAF mutations by tumor histology and location

Molecular therapeutic targeting

FIGURE 1 | Novel targeted agents and the pathways inhibited in solid tumors.

Penman, 2015, Frontiers in Oncol, 5, 54
Patient TN treatment course

Age 3:
Initial diagnosis with subtotal resection
Treated with Carboplatin, Vincristine, Temozolamid e

Age 8:
Relapse/progression
Treated with Vincristine, Dactinomycin

Age 10:
Relapse/Progression with biopsy showing KIAA1549-BRAF fusion
Treating with Irinotecan and Bevacizumab
MEK or mTOR inhibitor? XRT?
Patient TN comorbidities and late effects

• Left sided hemiparesis
• Poor speech articulation
• Broad neurocognitive weaknesses
  • General intellectual reasoning
  • Memory
  • Cognitive efficiency
  • Language processing
  • Motor coordination
Long term outcomes of childhood brain tumor survivors:

- CCSS cohort of 1887 adult survivors of childhood CNS tumors treated between 1970 and 1986 – retrospectively compared with sibling cohort
- 74% of children diagnosed with a CNS malignancy will become 5 year survivors
- Survivors of CNS malignancies are at the highest risk of late mortality
  - Primary disease 61%
  - Subsequent neoplasms 9%
  - Cardiac disease 3%
  - Pulmonary disease 3%
- 75% of survivors report having a chronic disease
- 42% report having a severe or life threatening condition
Chronic health conditions in 5-year survivors of CNS tumors

<table>
<thead>
<tr>
<th>Condition</th>
<th>PR† (95% CI)</th>
<th>HR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any condition</td>
<td>29.5 (23.8 to 36.6)</td>
<td>6.4 (5.4 to 7.5)</td>
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<tr>
<td>Endocrine complications</td>
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<td>Medication needed to initiate puberty</td>
<td>49.1 (27.6 to 87.2)</td>
<td>19.8 (14.5 to 27.1)</td>
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<td>Growth hormone deficiency</td>
<td>28.0 (6.7 to 117.8)</td>
<td>146.9 (35.4 to 608.8)</td>
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<td>Growth hormone injections</td>
<td>400.7 (56.2 to 2856.9)</td>
<td>140.4 (51.3 to 384.1)</td>
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<td>Hypothyroidism</td>
<td>267.6 (37.4 to 1912.5)</td>
<td>219.1 (54.5 to 880.5)</td>
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<td>Neurological complications</td>
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<tr>
<td>Weakness in arms or legs</td>
<td>31.4 (16.0 to 61.6)</td>
<td>13.0 (9.2 to 18.3)</td>
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<td>Decreased sense of touch, feelings in hands,</td>
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<tr>
<td>fingers, arms, or legs</td>
<td>37.1 (28.3 to 48.7)</td>
<td>5.6 (4.8 to 6.7)</td>
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<td>Prolonged pain or abnormal sensations in</td>
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<tr>
<td>arms, legs, or back</td>
<td>82.9 (41.2 to 166.9)</td>
<td>12.2 (9.1 to 16.3)</td>
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<tr>
<td>Problems with balance</td>
<td>82.9 (41.2 to 166.9)</td>
<td>12.2 (9.1 to 16.3)</td>
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<td>Seizures</td>
<td>45.7 (23.4 to 89.0)</td>
<td>3.9 (3.0 to 5.1)</td>
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<td>2.4 (1.9 to 3.0)</td>
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<tr>
<td>arms, legs, or back</td>
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<td>Problems with balance</td>
<td>102.7 (59.5 to 177.4)</td>
<td>18.0 (13.4 to 24.1)</td>
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<td>Sensory complications</td>
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<td>Cataract</td>
<td>30.8 (19.4 to 48.9)</td>
<td>15.1 (10.7 to 21.2)</td>
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<tr>
<td>Tremor or movement problems</td>
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<tr>
<td>Paralysis</td>
<td>75.2 (35.5 to 159.2)</td>
<td>15.0 (10.1 to 22.4)</td>
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<td>Sensory complications</td>
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<td>Hearing loss/deafness</td>
<td>73.9 (32.9 to 166.2)</td>
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<td>Blindness</td>
<td>35.3 (22.3 to 55.9)</td>
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Psychiatric conditions in brain tumor survivors

• 20% of survivors report depression
• 20% of survivors report anxiety
• Those having received radiation are at highest risk in addition to glial tumor type and female gender
• ~30% of survivors reports specific behavior problems including irritability and aggression
Neurocognitive/Sociodemographic outcomes

- Impairment in **attention and/or processing speed, memory, organization, and emotional regulation** in an RT dose-response pattern
- Having had a CNS tumor negatively alters **self perception and social intelligence**
- RT to frontal or temporal lobe of 50 Gy or higher was significantly associated with **unemployment**
- RT to any region associated with **never being married**
- RT to any region associated with **annual household income of $20K or less** in a dose-response pattern
Survivorship Program: KITE clinic and

At the KITE Clinic, a team of experts create personalized plans and provide ongoing services to help manage long-term or chronic conditions related to cancer or its treatment. Nannette Richard, M.D., (left), pediatric hematologist oncologist and Elissa Pocza, CPNP, CPON, (below right), are leading the clinic.

Eligibility
The KITE Clinic is open to children and families who have been off cancer therapy for at least two years, including adults who are survivors of childhood cancer. KITE Clinic visits are usually covered by insurance but do require a referral and pre-authorization. Survivors of childhood brain or spinal cord cancers receive specialized services through the Randall Children's Neuro-Oncology Clinic.

KITE Clinic services
The KITE Clinic provides a variety of services that address the physical health, mental and emotional health, and school and work needs of these cancer survivors. There is a coordinated team of experts at the clinic, as well as referrals to other knowledgeable about the specific needs of childhood cancer survivors.

Expertise in pediatric neuro-oncology

Randall Children's Hospital offers coordinated, compassionate care
For pediatric patients with tumors of the brain and spinal cord, we offer coordinated and compassionate care to meet the complex needs of these patients and their families, from diagnosis to personalized management and advanced treatment. Our goal is improving the survival rate and quality of life for these children through the most advanced, research-based care.

Every patient is seen in our comprehensive, multi-disciplinary clinic that bring together the sub-specialists to provide follow-up care to patients in a single visit.

Multidisciplinary care
We discuss each child's care at bi-monthly neuro-oncology tumor board reviews of pathology and neuro-imaging and at monthly multidisciplinary meetings. The result of this ongoing communication is a tailored treatment and follow-up plan that takes into account the needs of each patient and family.

Program components
- The only pediatric inpatient rehabilitation program in Oregon, including an on-site rehabilitation physician, physical therapist, occupational therapist and speech therapist.
- Highly regarded radiation oncologists with Gamma Knife stereotactic radiosurgery capabilities.
- Access to leading treatments and therapies through clinical trials offered by the Children's Oncology Group, a worldwide cooperative clinical trial group supported by the National Cancer Institute (NCI).

Care for the whole child
- Inpatient child life therapy and school support.
- Dedicated social worker to provide emotional and practical support and resources for patients and families.
References


Thank you!