Sarcomas

Living Beyond Cancer A-Z
UT Health San Antonio MD Anderson Cancer Center

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Bone and Soft Tissue Sarcomas

• Rare Tumors

• Different than “carcinoma”

• Cancers that start IN the tissues (cartilage, bone, muscle, tendon, ligaments, blood vessels)

• Unique management focused on multi-disciplinary approach
Bone and Soft Tissue Sarcomas

• Account for about 1% of all adult malignancies
  • Roughly 12,000 new diagnoses in United States in Adults

• Account for about 10% of all pediatric malignancies
  • Approximately 1,000 new diagnoses in United States
Diagnosis

• Many sarcomas misdiagnosed initially as benign tumors

• Requires pathologist with familiarity in sarcomas
  - 100’s of different sarcoma subtypes

• Biopsy should be done under supervision of surgeon that will be the ultimate treating surgeon
Sarcoma Principles

• Biopsies do not make cancers spread to other parts of the body

• Pathology analysis of the tissue can take 10-14 days for definitive results

• After diagnosing “what” it is, the next question: “where is it?”

• Most sarcomas when they metastasize will travel to the lungs
  Only a few will travel to lymph nodes
  CT of the Chest along with an MRI of the area of concern are necessary imaging tests
Sarcoma Principle

All sarcomas should be treated by a multi-disciplinary team and discussed at a specialized tumor board

UT Health Sarcoma Tumor Board
Rajiv Rajani MD, Robert Quinn MD – Orthopaedic Oncology
Frederico Tozzi MD, Mio Kitano MD – Surgical Oncology
Elizabeth Bowhay Carnes MD, Vinu Madhusudhanannair-Kunnuparampil MD (Madhu) – Medical Oncology
Aaron Sugalski DO – Pediatric Medical Oncology
Richard Crownover MD – Radiation Oncology
Josephine Heim-Hall MD – Pathology
Michael Tall MD, Michael Davis MD - Radiology
Sarcoma Treatment

Almost all sarcomas receive a surgery that removes the entire tumor.

Some patients will receive chemotherapy and radiation therapy based on a variety of factors:
- Appearance under microscope
- Present elsewhere
- Size of tumor
- How close to blood vessels, nerves, bone
Goals of Treatment

• Remove ALL tumor

• Retain highest level of function while minimizing tumor recurrence risk

• Pain free function

• Avoid future complications (fracture, infection, drainage, recurrence)
Examples
New Drug Development

- Standard cytotoxic chemotherapy includes Ifosfamide, Doxorubicin, Cisplatin, Methotrexate, Etoposide, etc.
- Genomics and tumor profiling has led to development of more molecular targeted therapies and precision medicine trials

- Anti-Angiogenic Drugs
  - Pazopanib – VEGFR, PDGFR, other TKIs
    - First FDA approved molecular targeted therapy for STS
  - Sunitinib (ASPS), Sorafenib, Regorafenib
  - Monoclonal Antibody - Olaratumab (PDGFR -)
    - Recent FDA approval for relapse disease
  - Anti-mitotic agent - Eribulin – advanced liposarcoma
New Drug Development

- DNA binding block – Trabectedin- advanced liposarcoma or leiomyosarcoma
- mTOR inhibitors – sirolimus, everolimus, temsirolimus
- ALK (anaplastic lymphoma kinase) inhibitor
  - Crizotinib – Inflammatory myofibroblastic tumor (IMT)
- TRK fusion inhibitor
  - Larotrectinib – STS with identified TRK
- Insulin-like growth factor 1 inhibitor – Trial for Ewing Sarcoma ongoing
- RANK ligand inhibitor – Denosumab for giant cell tumor
Immunotherapy Drug Development

• Checkpoint inhibitors (PD-1/PD-L1, CTLA-4) –
  • “Taking the brakes off the immune system”
  • Thought to be beneficial in tumors with high expression of PD-L1 or high mutational burden
  • Limited success at this point besides in undifferentiated pleomorphic sarcoma (UPS) or dedifferentiated liposarcoma
  • Pembrolizumab, Nivolumab, Ipilimumab, others
Immunotherapy Drug Development

- Genetically Engineered Specific T Cells
  - NY-ESO-1 - synovial sarcoma; myxoid/round cell liposarcoma
- Chimeric Antigen Receptor (CAR) T cell – Target HER2 (osteosarcoma)

- Vaccines – utilize tumor-specific fragment to trigger immune system to target cancer cells
  - NY-ESO-1 trials; SYT-SSX for synovial sarcoma
  - Early stages of development and likely need to be combined with other therapies (radiation, chemotherapy, checkpoint inhibitors)
Greehey Children’s Cancer Research Center (GCCRI) Sarcoma Team

- Alex Bishop – Ewing sarcoma DNA Damage Repair.
- Peter Houghton – Insulin-like Growth Factors and Developmental Therapeutics Ewing sarcoma and rhabdomyosarcoma.
- Raushan Kurmasheva – Ewing sarcoma, Developmental Therapeutics.
- Yuzuru Shiio – Biology of Ewing and Synovial Sarcoma.
- Manjeet Rao – Osteosarcoma.
- David Libich – Fusion oncogenes, Ewing and synovial sarcoma.
Zebrafish Models of Cancer/Sarcoma

In vivo Imaging

Relapse assays:
High-throughput Cell Transplantation

Bioinformatics Approaches

Zebrafish Models Sarcoma

Genetic approaches:
- Transgenesis
- Loss-of-function

Chemical Genetic Approaches

Mosaic Transgenic

30 dpf
November 12-13, 2018 • Merck Research Laboratories
33 Avenue Louis Pasteur Boston, MA

PAWS FOR A CURE RESEARCH SYMPOSIUM

Translational Potential Of Comparative Approaches To Accelerate Drug Development In Shared Childhood & Canine Cancers

WHO SHOULD ATTEND:
- Pediatric oncologists
- Veterinary oncologists
- Translational research scientists in academia and in industry
- Pharma and biotech professionals in preclinical research, drug development, oncology and animal health
- Nonprofit and other funders interested in learning about comparative and translational approaches to accelerate development of new and better medicines for the treatment of cancer, particularly devastating shared childhood and canine cancers.

Co-hosted by

CANINES-N-KIDS FOUNDATION  MERCK INVENTING FOR LIFE

ADVANCING RESEARCH IN PEDIATRIC CANCER TREATMENTS has unique challenges, and progress toward better medicines and a cure has been limited. Intriguingly, BOTH children and our canine companions spontaneously develop a number of cancers with remarkable similarities, including osteosarcoma, certain brain/CNS cancers, lymphoma and leukemia. Speakers, panelists and participants will discuss challenges and progress in accelerating cancer drug development using comparative approaches, including:

- The state of the art in comparative and novel translational cancer research
- Ongoing preclinical, translational and clinical projects leveraging the canine patient model.
- The most promising prospects for future scientific exploration, collaboration and funding.
- Life journey presentations by childhood cancer survivors and advocates.

EARLY BIRD REGISTRATION SAVINGS AVAILABLE!
Sarcoma Survivorship

• Sarcoma treatment is combination of surgery, radiation, chemotherapy, or immunotherapy.
• Requires follow up in multi-disciplinary clinic for long term effects of treatment
### TABLE I. Late Effects in the STS Survivor by Exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Organ system</th>
<th>Specific late effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Doxorubicin</td>
<td>Cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pediatric: Dilated followed by restrictive cardiomyopathy</td>
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<tr>
<td></td>
<td></td>
<td>Adult: Dilated cardiomyopathy Arrhythmia</td>
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<tr>
<td></td>
<td></td>
<td>Diabetes, HTN, lipid disorders, CAD</td>
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<tr>
<td>Ifosfamide</td>
<td>Renal toxicity</td>
<td>Fanconi syndrome; growth inhibition; Nephrogenic Rickets</td>
</tr>
<tr>
<td>Secondary malignancy (SMN)</td>
<td></td>
<td>Secondary leukemia at high cumulative dose as well as secondary solid malignancy in rare instances</td>
</tr>
<tr>
<td>Fertility complications</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Cisplatin                 Hearing Loss
- Methotrexate              Renal Toxicity, Neurotoxicity
- Cyclophosphamide          Renal Toxicity
- Etoposide                 Secondary Malignancy
- Any                       Anxiety, Depression
<table>
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<tr>
<th>Exposure</th>
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<th>Specific late effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>Renal toxicity</td>
<td>Radiation induced Nephropathy (Dose 20–25 Gy)</td>
</tr>
<tr>
<td></td>
<td>Fertility complications</td>
<td>STS patients unlikely to receive primary gonadal radiation but azospermia is documented at doses above 4 Gy in men and ovarian failure at doses above 8 Gy in women</td>
</tr>
<tr>
<td>Radiation,</td>
<td>Secondary malignancies</td>
<td>STS patients are at increased risk for solid tumors in the field of radiation</td>
</tr>
<tr>
<td>continued</td>
<td>Musculoskeletal complications</td>
<td>Pediatrics: Growth arrest at doses above 10–20 Gy if epiphyseal growth plate is within the radiation field; Spinal deformity, craniofacial defects, slipped capital femoral epiphysis, limb length discrepancy depending on dose, volume, and field of radiation ALL: Osteopenia: Muscle, bone, and soft tissue hypoplasia; Strength deficit, Rarely muscle atrophy and edema which can lead to long term fibrosis and chronic pain</td>
</tr>
<tr>
<td>Surgery</td>
<td>Functional and musculoskeletal complications</td>
<td>Dependent on area and extent of resection</td>
</tr>
</tbody>
</table>
Chronic Health Conditions in Adult Survivors of Childhood Cancer


Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Survivors (N = 10,397)</th>
<th>Siblings (N = 3034)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major joint replacement*</td>
<td>1.61</td>
<td>0.03</td>
<td>54.0 (7.6–386.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.24</td>
<td>0.10</td>
<td>15.1 (4.8–47.9)</td>
</tr>
<tr>
<td>Second malignant neoplasm†</td>
<td>2.38</td>
<td>0.33</td>
<td>14.8 (7.2–30.4)</td>
</tr>
<tr>
<td>Cognitive dysfunction, severe</td>
<td>0.65</td>
<td>0.10</td>
<td>10.5 (2.6–43.0)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.11</td>
<td>0.20</td>
<td>10.4 (4.1–25.9)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1.56</td>
<td>0.20</td>
<td>9.3 (4.1–21.2)</td>
</tr>
<tr>
<td>Renal failure or dialysis</td>
<td>0.52</td>
<td>0.07</td>
<td>8.9 (2.2–36.6)</td>
</tr>
<tr>
<td>Hearing loss not corrected by aid</td>
<td>1.96</td>
<td>0.36</td>
<td>6.3 (3.3–11.8)</td>
</tr>
<tr>
<td>Legally blind or loss of an eye</td>
<td>2.92</td>
<td>0.69</td>
<td>5.8 (3.5–9.5)</td>
</tr>
<tr>
<td>Ovarian failure†</td>
<td>2.79</td>
<td>0.99</td>
<td>3.5 (2.7–5.2)</td>
</tr>
</tbody>
</table>

Slide adapted from Dr. Gregory Aune

Oeffinger et al., NEJM, 2006
Studied 5,522 Survivors ≥18 years old and ≥ 10 years form diagnosis

On average:

- 17.1 chronic health conditions grade 1-5 by age 50
- 4.7 chronic health conditions grade 3-5 by age 50
Cumulative burden of chronic health conditions by disease

Figure 3: Cumulative burden of severe (grade 3-5) chronic health conditions in St Jude Lifetime Cohort Study survivors of childhood cancer and in community controls

Sarcoma Survivorship at UT Health San Antonio

- Pediatric, Adolescent and Young Adult (AYA) Diagnosis
- Musculoskeletal Tumor Follow-up Clinic
- Multidisciplinary visit seen by Pediatric Oncologist, Orthopedic Oncologist, Prosthetist, Psychologist.
- Screened with recommended Imaging, ECHO/EKG, Audiogram and Laboratory Assessments
- Appropriate referrals completed
- Research Studies offered through Children’s Oncology Group
  - ALTE11C2 - Health Effects after Anthracycline and Radiation Therapy (HEART)
  - ALTE1621- Pharmacologic Reversal of Ventricular Remodeling: A Phase 2b Randomized Placebo-Controlled (Carvedilol) Trial
  - ALTE16C1- Effects of Modern Chemotherapy Regimens on Spermatogenesis and Steroidogenesis in Adolescent and Young Adult (AYA) Survivors of Osteosarcoma
Issues experienced and support provided to adolescents and young adults at the end of active treatment for cancer: A rapid review of the literature

Table 3: Sources of information and support for young people with cancer at the end of active treatment

<table>
<thead>
<tr>
<th>Source</th>
<th>Key things recommended or identified as sources of support/information</th>
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</table>
| Hospital/medical team         | • Post-treatment support provided by the hospital, by professionals such as social workers and specialist nurses (Moody et al., 2015)  
• Preparation for end of treatment, provision of information, follow-up and service referrals after treatment ends; longer consultations than older cancer patients (Brédart et al., 2015)  
• Sleep screening to identify disturbances and better support to adolescents and young adults (AYA) after completion of cancer therapy are important to reduce impact of poor sleep (Daniel et al., 2017)  
• Provision of a summary at the end of treatment, to facilitate AYA when telling others about their cancer when they return to school (Choquette et al., 2016)  
• Effective communication between the school and hospital before active treatment ends, to assist smooth reintegration to school (Thompson et al., 2009)                                                                                                                   |
| Family and existing friends and peers | • Maintaining peer groups or close friendships throughout treatment (Choquette et al., 2016; Pini et al., 2013)  
• Family was reported by healthcare professionals as one of the main sources of support for young people after treatment ends (Moody et al., 2015)                                                                                                                 |
| Peers with cancer             | • Opportunities and mechanisms for peer-to-peer support and to connect with other AYA living with and beyond cancer, for example support groups specifically for AYA, peer-to-peer counselling (Moody et al., 2015; Roper et al., 2013; Thompson et al., 2009)                                                                                       |
| Online                        | • Access to cancer websites and social media groups online to access social support (Moody et al., 2015; Shen et al., 2016)                                                                                                                                                                                                                                      |
| Specific services             | • Programmes targeting health behaviour, which covered nutrition and exercise, were used immediately after treatment and popularity increased at 6 months after treatment (Roper et al., 2013)  
• A rehabilitation programme providing psycho-education targeted at giving AYA tools to cope with the challenges of cancer survivorship (Hauken & Viken, 2015)  
• Use of cognitive therapy to help AYA cope with negative thoughts, emotions and behaviours (Hauken & Viken, 2015)                                                                                       |
| Education/work                | • Encouragement from teachers; in addition to maintaining relationships with school personnel throughout their treatment (Choquette et al., 2016; Pini et al., 2013)  
• Having a reduced school workload to help AYA transition back to school (Choquette et al., 2016)  
• Transitional care planning to assist AYA to re integrate through return-to-work assistance and occupational rehabilitation (Thompson et al., 2009)                                                                 |