Late Effects: After Therapy for Childhood Cancer

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Conflict of Interest

• None. I have no industry financial relationships.
Objectives

• Overview of:
  • Frequency of late effects in survivors of pediatric cancer
  • Late effects caused by:
    • Disease
    • Therapy:
      • Surgery
      • Chemotherapy
      • Radiation Therapy (RT)
  • Multiple different organ systems at risk

• Identify:
  • Major long term health problems in this population
  • The impact of these problems on survivor’s life
  • Health care implications
Incidence

- About 10,400 children in the US (between birth and 14 years of age) develop childhood cancer each year.
- In Canada, 1,310 patients diagnosed with cancer between the ages of 0 and 19 per year.
- 80% of these children will be long term survivors who have been cured of their disease.
- 20 to 30 years ago many children with cancer did not survive.
- Improvements due to:
  - Multimodality Rx
  - Therapy intensification
- In 2010 - estimated that 1:250 of the adult population in North America will be a survivor of childhood cancer.
Survivorship

- **Cancer survivor:**
  - One who remains alive and continues to function during and after overcoming a serious hardship or life-threatening disease.
  - In cancer, a person is considered to be a survivor from the time of diagnosis until the end of life.

*Ellen Stovall*: CEO of the National Coalition for Cancer survivorship
Late Effects

• Definition:
  • “Side effects that occur more than 5 years after diagnosis”
• Problems with definition:
  • Etoposide related AML (short latency)
• Generally takes many years for late effects to develop
• How are these problems detected?
  • Follow up
    • Surveillance programs – clinic or mail contact
• How can we reduce these risks?
  • Initial treatment modality and patient selection
  • Awareness of long term health risks
    • Patients
      • Life style choices – smoking, diet, exercise, screening
    • Health care professionals
      • Do the correct investigations
Late Effects

- 60% of childhood cancer survivors will have at least one late effect
- Survivors of CNS tumors are most likely to be functionally impaired
Organs at Risk

- Central nervous system
  - Brain
  - Spine
- Orbit
- Hearing
- Peripheral Nervous system
- Endocrine
- GU system
- Respiratory
- Gastro-intestinal
- Musculoskeletal
- Reproductive organs
- Cardiovascular
Tumor Related Damage

- Invasion into and pressure on different structures
  - **Wilms tumor**
    - One kidney usually completely destroyed by disease and has to be removed
Tumor Related Damage

- **Craniopharyngioma** tumor growth and cyst expansion leads to compression of:
  - Optic apparatus
    - Blindness
  - Pituitary
    - Endocrinopathy
Surgery Related Damage

- Surgery
  - Prime modality for local control
- Lymph node dissection
  - Lymphedema
- Splenectomy
  - Life threatening infection
    - Pneumococcal vaccine
    - Medic Alert bracelet
Chemotherapy Related Damage

- Chemotherapy prime modality for systemic control
- Depends on agent and sensitivity of target organs
  - Adriamycin – cardiomyopathy
  - Cisplatin – nephrotoxicity and hearing loss
  - Alkylating agents – infertility and second cancers
  - Vincristine and peripheral neuropathy
Radiation Therapy (RT)

- In children (unlike adults) affects normal growth/development
- Toxicity depends on:
  - Age at the time of therapy
  - Total dose given
  - Fractionation
- Region treated:
  - Some organs more sensitive and easily damaged
  - Amount of normal tissue treated
- Concurrent chemotherapy can sensitize normal tissues
- Underlying genetic problems
  - Ataxia-telangectasia
  - Radio-genomics
CNS

• Brain
  • Developmental delay
  • Poor short term memory
  • Poor executive function
  • Seizures
  • Cerebrovascular events
    • Thrombotic and haemorrhagic
• Spinal cord
  • Myelitis
• Hearing loss
• Visual loss
CNS: Leukemia

- Brain: “leukoencephalopathy”
- Damage to white matter of brain
- Linked with:
  - Whole brain RT
  - IT Methotrexate
  - High dose IV Methotrexate and Ara-C
- Increased risk of neurocognitive deficits:
  - Higher doses of RT
  - Rx with both cranial RT and systemic/IT chemo
  - Young age at Rx
  - Female gender
  - School absence
  - Pre-treatment intellectual status
CNS: Leukemia

- **Leukoencephalopathy** MR changes:
  - Periventricular “halo” or band of hyperintensity
  - Variable thickness
  - Forms smooth lateral margins around the ventricles
CNS: Brain Tumors

- Long term IQ in pediatric brain tumor patients depends on age at the time of therapy:
- Age at time of therapy for medulloblastoma:
  - 1–5 years:
    - Mean IQ of 72
    - 50% of patients had scores less than 80
  - 6–10 years:
    - Mean IQ of 93
    - 14% had IQ scores of less than 80
  - Children 11- 15 years:
    - Mean IQ of 107
    - 9% had IQ scores of less than 80
Orbit

- Visual loss
  - High dose RT:
    - Anterior chamber damage
    - Acute glaucoma
    - Painful red eye
    - Treated by enucleation
  - Low dose RT:
    - Cataracts
Hearing loss

- Radiation Therapy:
  - Conductive: wax build up
  - Sensorineural: direct damage to cochlea
- Chemotherapy:
  - Sensorineural
  - Cisplatin causes high frequency hearing loss
    - Sensory hair cells in the cochlea
Musculoskeletal

- Bone/Muscle/soft tissues
  - “Hypoplasia” – reduced growth within the RT field
Facial Hypoplasia

- Lucy Grealy “ Autobiography of a face”
Musculoskeletal

- Bone/Muscle/soft tissues
  - Hypoplasia – reduced growth within the RT field
  - Endocrinopathy
Endocrinopathy

- Pituitary dysfunction
  - GH
  - TSH
  - FSH & LH
  - ACTH
- Thyroid damage
  - Primary Hypothyroidism
Cardiovascular disease

• 10 – 15% of all cardiomyopathies in young adults related to previous treatment for cancer
• Cardiac injury is a significant cause of mortality and morbidity in cancer survivors
  • 10X risk compared to general population
• Cardiopulmonary disease is the 3rd most common cause of death for patients after treatment for a pediatric malignancy
• For long-term survivors of childhood cancer:
  • First cause of death: Recurrence of the primary malignancy
  • Second cause of death: Second malignancy
  • Third cause of death: Cardiac Injury
Cardiovascular disease

- Etiology: Adriamycin and RT
  - Adriamycin:
    - Dose related cardiomyopathy
  - Mediastinal RT for Hodgkin lymphoma (HL): 5% of patients have symptomatic heart disease 10 years later
    - Cardiomyopathy
    - Coronary artery disease
    - Pericarditis
    - Valvular disease
    - Conduction system problems
      - AV and bundle branch block
  - Neck RT: Vascular problems
    - Carotid artery disease
- Hypertension
GU/Renal disease

- Kidneys especially vulnerable
- Chemotherapy
  - Cisplatin
    - Magnesium-wasting tubulopathy
  - Ifosfamide
    - Proximal tubular dysfunction and less frequently decreased GFR
  - Methotrexate
    - Acute renal dysfunction
- RT
  - Doses greater than 20 Gy result in significant nephropathy
- Surgery
  - Reduction in renal tissue
- Hypertension
Pulmonary disease

- Lungs very sensitive to both RT and chemotherapy
- Bleomycin:
  - Intra-alveolar exudates with subsequent organization
  - Hyaline membrane formation
  - Interstitial fibrosis
  - Atypical proliferation of alveolar cells
- RT:
  - Pneumonitis
  - Chest wall deformity – restrictive defect
Chest wall deformity:
GI disease

• Intestines very sensitive to RT:
  • Malabsorption
  • Strictures
  • Adhesions and obstruction
  • Fistula
• Previous surgery increases risk
Reproductive system

- Gonads very sensitive to both RT and chemotherapy
  - Alkylating agents
  - RT to ovaries:
    - The dose of RT needed to destroy 50% of the oocytes = LD50
    - Oocytes are very sensitive with an LD50 of < 200 cGy
- Damage to developing uterus
Secondary tumors

- Significant long term risk for any child who has RT
  - 8-10% risk of second malignancies within 20 years
  - 5-20 X greater than general population (Friedman et al. Pediatric Clin North Am 2002)

- Childhood Cancer Survivor Study
  - N= 13581
  - Found 314 SMN in 298 individuals
  - 20 yrs post diagnosis risk was 3.2% (Robison)

- Risk Factors:
  - Age at primary malignancy
  - Chemotherapy/RT
  - Genetic predisposition
  - Time since original malignancy (risk increases as cohort ages)
Secondary tumors

• Most common:
  • Breast
    • High risk in adolescent females given mantle RT for Hodgkin lymphoma
    • Occurs at young age (less than age 40)
    • Early and increased screening critical
  • Bone
  • Thyroid
  • MDS and AML
    • Alkylating agents and topoisomerase II inhibitors
    • 5-10 years post treatment after alkylating agent
    • Shorter latency after topoisomerase inhibitors
    • Risk plateaus after 10 years
    • Prognosis poor
  • CNS
Secondary tumors

- **RT induced meningioma**
  - Multiple
  - Atypical
  - More likely to recur after surgery
Second Malignant Neoplasm
Psychosocial

• Increased risk for survivors of problems with:
  • Education
    • Special programs, teaching aids
  • Employment
    • Vulnerable to discrimination
    • Getting a job (32% survivors rejected vs 19% siblings)
    • Military service (80% rejected vs 18% siblings)
  • Insurance
    • Previous serious illness with long-term health risks
    • Difficult to legislate
    • Contracts entered into freely by individual and company
    • Parties should be free to create their own terms
  • Social isolation
  • Mental illness
    • Increased incidence of depression
Psychosocial

• Many brain tumor survivors:
  • Need very modified school curriculum
  • Rely on permanent disability pension:
    • Differences across the province and between different provinces regarding available programs
      • Access to vocational/recreational rehab
  • Drug costs covered by parents benefits plan
  • Other costs not covered:
    • Hearing aids
BCCA Study

• Preliminary results on 24 pediatric brain tumor survivors:
  • 90% graduated from high school
  • 42% of parents did not think their child received adequate support at school
  • 82% bullied by peers
  • 53% bullied by school staff
  • 63% had difficulty getting or keeping a job after school
  • 58% unable to cover daily living expenses without parental support
  • 71% of parents pay for their child’s medical expenses out of pocket
  • 27% victim of theft, assault or fraud
Impact on Life

• Huge range of late effects:
  • Low risk:
    • Many (but not all) previous lymphoma and leukemia patients
    • Function very well
  • High risk:
    • Brain tumors and solid tumors like sarcomas
    • Lives may be “devastated”
• Long term health care:
  • Counseling
  • Screening/Surveillance for late effects
Counseling

• Lifestyle:
  • Diet
  • Exercise
  • Smoking/recreational drugs
  • Sun/UV exposure
Screening

• Follow up care depends on “risk category”
  • High risk: Hospital based and family practitioner
  • Low risk: Family practitioner

• Survivorship Care Plan:
  • Coordinated post-treatment plan
  • Built by survivor’s oncology team
  • Includes
    • Summary of the survivor’s treatment
    • Direction for future care

• Screening recommendations: COG Long Term FU Guidelines
Informed Consent

• Communication of long-term health risks at the time of diagnosis
• Is “true informed consent” ever possible?
  • Nature of information:
    • “Foreign” and complex
    • Vast quantity
    • Clinical trials
    • Bias in the way information is presented
  • Emotional overlay
  • Time to make decision short
• Legal standards mandated rarely achievable
• How best to convey that information
Resources

• COG: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers
Resources

• National Cancer Institute: Late Effects of Treatment for Childhood Cancer
Children and adolescents account for about 4% of all new cancer cases annually, and the number of childhood cancer survivors has increased significantly over the past decades. Children and adolescent cancer treatments, prevention, diagnosis, surveillance, and survivorship have become increasingly complex and require specialized care. These patients may require specific cancer survivorship care, which includes both physical and mental health concerns. This care is provided by medical, psychosocial, and support services.

Pediatric Oncology Education Materials

**Late Effects**

On average approximately 10,400 North American children (between birth and 14 years of age) develop childhood cancer each year and these numbers seemingly increase annually.

More than 80% of these children will be long term survivors who have been cured of their disease. This was very different 20 to 30 years ago, when many children did not survive.

In general, cure rates have been improved by using:

- Multiple treatment modalities
  - Radiation therapy (RT)
  - Chemotherapy
  - Surgery
- Therapy intensification (using higher total doses of chemotherapy over a shorter period of time)
- Improved supportive care
Thank you!