Late effects of childhood cancers

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Incidence of childhood cancers

- 300,000 children develop cancer each year – WHO statistics
Distribution of childhood cancers - US statistics
Childhood cancer survivors are living longer - more late effects manifest.
Impact of new chemotherapy in ALL

Pui, NEJM 1995; 332: 1618
Background

- High income countries – 80% cured
- LMIC -20% cures
- Cure – early diagnosis, multimodal treatment

- Multimodal Cancer directed therapy is toxic
- Children – growing organs – vulnerable
- Preventable/ reduced severity

Oeffinger et al NEJM, 2006
Our current approach to childhood cancers
While most late effects are not life-threatening, they may cause serious problems that affect health and Quality of Life.
Late effects – tumor related factors

- Type of cancer.
- Site
- Stage of tumor (adjacent organ involvement)
- Genetic and familial conditions
Late effects – treatment related factors

– Type of surgery.
– Chemotherapy type, dose and schedule
– Type of radiation therapy, part of the body treated, and dose.
– Stem cell transplant.
– Use of two or more types of treatment at the same time.
– Chronic graft versus host disease
Late effects - Patient related factors

- Gender
- Baseline Health
- The child’s age at diagnosis.
- Length of time since diagnosis and treatment.
- Immune status and repair capacity
Treatment modality

- Surgery
- Radiotherapy
- Chemotherapy
- Bone marrow transplantation

Each modality has its own acute and late side effects.
Peculiarities of childhood cancers - radiation

- Children have lower tolerance to radiation due to growing tissues and therefore likely to suffer more damage
- Relatively large target volumes compared the overall body volume
- Immobilization of young children is a major issue
- May require anaesthesia
- Additional dose limits
## Dose limits children versus Adults

<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>CHILD RT LIMITING DOSE</th>
<th>ADULT RT DOSE LIMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>18 Gy</td>
<td>35 Gy</td>
</tr>
<tr>
<td>Bones</td>
<td>10 Gy</td>
<td>&gt; 65 Gy</td>
</tr>
<tr>
<td>Pituitary (GH)</td>
<td>20 Gy</td>
<td>NA</td>
</tr>
<tr>
<td>Ovary / Testes</td>
<td>10 Gy</td>
<td>NA</td>
</tr>
<tr>
<td>Breast CA Induction at 40 Gy</td>
<td>RR = 20</td>
<td>RR = 2</td>
</tr>
<tr>
<td>Lung MLD</td>
<td>&gt; 9 Gy</td>
<td>17 Gy</td>
</tr>
<tr>
<td>Lens (cataract)</td>
<td>&gt; 12-15 Gy</td>
<td>&gt;10-12 Gy</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Below 20 Gy up to 14 yrs age</td>
<td>NA</td>
</tr>
</tbody>
</table>
Cumulative mortality of childhood cancers
Survivorship - Living beyond cancer

- 2-5 years off therapy and free of disease
- Long term/late effects of illness for the child
- Long term effects of treatment
- What family (parents and sibling) experience - rehabilitation

Mullan’s survivorship seasons

Acute
Extended
Permanent
Late effects

- Unrecognized toxicities that are absent or subclinical at the end of therapy – manifest later with unmasking of hitherto unseen injury
- Why does it manifest now?
  - Development process
  - Failure of compensatory mechanism
  - Organ senescence

Long term side effects – persistence of effects that appear during therapy and continue there after

Late effects – effects that appear months and years after treatment
Types of late effects

- System specific – organ damage or failure
- Second Malignant neoplasm
- Recurrent/ cancer assoc with primary
- Cancer assoc with therapy
- Functional changes
# Cardiac late effects

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Myocardial damage; CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>Atherosclerosis, Valvular disease, Pericardiac effusions/ constrictive disease</td>
</tr>
</tbody>
</table>

**Anthraclycline** → **Kill myocyte** → **↓ Cardiac function**  
**Arrhythmia**  
**Heart failure**  
**Dose dependence**  
**Median time of onset – 7 years**
Neuro cognitive late effects

- Whole Brain
- Intra-thecal Methotrexate

- High risk
- Higher dose
- Younger age <6yrs
- Females

Destruction of white matter
Reduced scholastic performance
Onset – several years ➞ Progressive
## Educational issues

<table>
<thead>
<tr>
<th>Radiotherapy to brain &amp; chemotherapy</th>
<th>Affect learning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation treatment</td>
<td>Short term memory loss – decline in scholastic performance</td>
</tr>
<tr>
<td>Absence from school; avoidance of peers</td>
<td>Diminished performance</td>
</tr>
</tbody>
</table>
Psychological issues

- 1/5th – Post traumatic stress disorders
- 1/4th – Depression/anxiety
- 1/3rd – Long term psychological issues; suicidal ideations

- Fear of recurrences
- Adjustment of late effects
- Financial issues
- Sexual issues
- QOL issues
Pulmonary late effects

<table>
<thead>
<tr>
<th>Chemotherapy (Bleomycin)</th>
<th>Dose dependent Pulmonary scarring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy (Dose dependent)</td>
<td></td>
</tr>
</tbody>
</table>

Combination (CT+RT) aggravates

Infection, Intra-operative Oxygen, Age

Premature respiratory insufficiency

Onset 1 to 7 years
Growth and development

• Total dose, fraction size, volume treated and age of radiation treatment affect ultimate height
• Steep dose-effect relation ship for bone growth – between 15-30Gy
• Cranial irradiation – early puberty – reduce ultimate height
An example – Wilms Tumor

• Flank RT – 1080cGy/6fr – Stage III disease
## Endocrine issues

<table>
<thead>
<tr>
<th>Obesity – dose dependent effect of cranial irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
</tr>
</tbody>
</table>

**Thyroid –**
HNC, HD RT
40-90% cases at 20yrs in doses >15Gy

Cranial irradiation - early onset of puberty
Poor linear growth – short stature
10 -15% survivors – below 5th percentile
Urinary effects

- Glomerular injury recovers
- Tubular injury persists – HT
- Radiation > 20Gy – tubular damage
  - shrunken bladder
- CT+RT dysfunction cutoff 10-15Gy

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Cisplatin, Ifosphamide, Methotrexate, NU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy (Flank)</td>
<td>Hypertension due to RT to the kidney</td>
</tr>
</tbody>
</table>
### Fertility issues

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy (Alkylating agents)</td>
<td>Reduced sperm production/ ovarian function</td>
</tr>
<tr>
<td>Radiotherapy (Abdominal RT)</td>
<td>Uterine shrinkage; Ovarian failure</td>
</tr>
<tr>
<td>Surgery (RPLND)</td>
<td>Retrograde ejaculation</td>
</tr>
</tbody>
</table>

- Delayed or impaired puberty
- Infertility
- Miscarriage
- Still birth
- Low birth weight babies

Gonadal failure or Infertility –
May be transient in males – dose dependent
Ovarian function recovery is poor
<table>
<thead>
<tr>
<th>Organ system</th>
<th>Late effects/sequelae of radiotherapy</th>
<th>Late effects/sequelae of chemotherapy</th>
<th>Chemotherapeutic drugs responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and soft tissues</td>
<td>Short stature; atrophy, fibrosis, osteonecrosis</td>
<td>Avascular necrosis</td>
<td>Steroids</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Pericardial effusion, pericarditis, CAD</td>
<td>Cardiomyopathy; CHF</td>
<td>Anthracyclines, Cyclophosphamide</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary fibrosis; decreased lung volumes</td>
<td>Pulmonary fibrosis; interstitial pneumonitis</td>
<td>Bleomycin, BCNU</td>
</tr>
<tr>
<td>Central nervous system (CNS)</td>
<td>Neuropsychologic deficits, structural changes, hemorrhage</td>
<td>Neuropsychologic deficits, structural changes</td>
<td>Methotrexate, Adriamycin, Methotrexate</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td></td>
<td>Hemiplegia; seizure</td>
<td>Cisplatin, Vinca alkaloids</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Cytopenia, myelodysplasia</td>
<td>Myelodysplastic syndromes</td>
<td>Alkylating agents</td>
</tr>
<tr>
<td>Renal</td>
<td>Decreased creatinine clearance</td>
<td>Decreased creatinine clearance</td>
<td>Cisplatin, Methotrexate, Nitrosoureas</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Increased creatinine clearance</td>
<td>Nitrosoureas</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Bladder fibrosis, contractures</td>
<td>Bladder fibrosis; hemorrhagic cystitis</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Malabsorption; stricture; abnormal LFT</td>
<td>Abnormal LFT; hepatic fibrosis, cirrhosis</td>
<td>Methotrexate, BCNU</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Growth hormone deficiency; pituitary deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>Hypothyroidism; nodules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental/oral health</td>
<td>Poor enamel and root formation; dry mouth</td>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Cataracts, retinopathy</td>
<td>Cataracts</td>
<td></td>
</tr>
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</table>
Second malignancy

- Chemotherapy (Alkylating agents; Epipodophyllotoxins)
- Radiotherapy
- Combination increases the risk further
- Genetic predisposition – HNPCC gene etc
- IMRT increases integral dose – Higher risk of SM

- Skin cancers, Bone and ST tumors - common
- Secondary leukemias, Colon cancers, Breast cancers – less common
- Average latency report – 15 years
- Increases with time
Cumulative incidence of developing SM with selected cancers

8-10% risk of developing SMN within 20yrs of primary diagnosis
Relative risk of Thyroid cancer by age & Radiation dose
Late recurrence

- A reality - different for different tumor types
- Fear lurks!
- 4.4% at 10 yrs
- 5.6% at 15 yrs
- 6.2% at 20 yrs

Childhood cancer survivor study report. Wasilewski et al JNCI2009
How to limit late effects

- Delay or omit Radiotherapy till the child is older
- Decrease Radiotherapy doses if possible
- Decrease volume of Radiotherapy portals
- Incorporate chemotherapy
- Alteration of Radiotherapy fractionation
- Use of novel techniques
Grading of late toxicity

- To systematically monitor the development/progression of late effects
- Impede development of toxicity related interventions
- Comparison between Institutions/ across clinical trials

NCI Common toxicity criteria
- Both acute and late effects
- Effects due to multimodal therapy
- Duration of an effect

Need follow up
Why follow up?

- Timely diagnosis of long term complications of cancer treatment
- Institute preventive strategies
- Screening and early detection of second malignancy
- Detection of Functional/Physical/ Psychological disability
How and what—follow up

- Regular physical examination and screening
- Physical growth
- Neurocognitive development
- Hormonal imbalance - puberty

When Do Late Effects in Childhood Cancer Survivors Cease Emerging? The Endocrine Answer

Mark L. Greenberg, The Hospital for Sick Children, The University of Toronto; and Pediatric Oncology Group of Ontario, Toronto, Ontario, Canada
DALY - Disability adjusted life years

- Common measurement unit for morbidity and mortality
- Comparisons of health outcomes
- Burden and Cost effectiveness
- Selection of intervention
- QOL reduced due to disability (QALY – Quality adjusted life years) OR
- Lifetime lost due to premature mortality
Outlook of survivor children

- Greater appreciation of life
- Lesser degree of aggression, antisocial behavior, substance abuse
Cure is not enough

Dr. Giulo D’Angio

- Aronyatesh Ganguly, cancer survivor won a gold medal

8-year-old cancer survivor bags gold in Moscow

Sumati Yengkhom | TNN | Updated: Jul 15, 2019, 17:38 IST
Summary

• Late effects are price that we pay to cure cancer
• Late effects are not “One size fits all”
• Today’s treatment strategies/ techniques look into the probability of late effects and how to decrease them
Thank you