Adverse effects of chemotherapy and radiotherapy

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ESMO Preceptorship on Adolescents and Young adults with cancer
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Adverse effects of treatment in AYA

- Defined as the effects of antineoplastic treatment (chemotherapy and radiotherapy) occurring during and after completion of treatment.

- A huge emerging issue as approximately three quarters of adolescents achieve long-term survival.

- Caused by the cancer, and the delivery of intense multimodality treatment to AYA.

- They can affect every aspect of patient’s health, quality of life and psychological well being.

Woodward et al 2011
Disabling surgery is a cause of late effects interfering with patient’s quality of life.

Mutilating surgery in the limbs, head and neck or torso causes disfigurement with resultant functional disabilities.

This may not always be necessary, such as limb-sparing surgery with modern endoprostheses has enabled preservation of functional limbs.

Hollis R et al. Lancet Oncology 2001
# Effects of Chemotherapy

## Table 2 Common late effects of cytotoxic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Late effect</th>
<th>Cumulative dose (mg/m²)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Cardiomyopathy</td>
<td>550</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cardiomyopathy</td>
<td>&gt;1550 daily for 3–4 days</td>
</tr>
<tr>
<td></td>
<td>Pulmonary toxicity</td>
<td>6500 in a few days</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Cardiomyopathy</td>
<td>160</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Cardiomyopathy</td>
<td>70 as monotherapy, 30 in combination with anthracycline</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Neurotoxicity</td>
<td>1000</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Pulmonary fibrosis</td>
<td>360 units</td>
</tr>
<tr>
<td></td>
<td>Skin pigmentation</td>
<td>270 units</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Pulmonary fibrosis</td>
<td>700 for Carmustine</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Busulphan</td>
<td>Pulmonary toxicity</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy</td>
<td>16 mg/KBΣ in a few days</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic fibrosis</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Neurotoxicity</td>
<td>16 mg within 4 months</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Myelodysplasia</td>
<td>2000</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Encephalopathy</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Pulmonary toxicity</td>
<td>16 g/m² within a few days</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity</td>
<td>20 g/m²</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Neurotoxicity</td>
<td>400–600</td>
</tr>
<tr>
<td></td>
<td>Renal toxicity</td>
<td></td>
</tr>
</tbody>
</table>

¹ Doses in mg/m² unless stated otherwise.

*Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007*
Effects of Chemo: 
Alkylation agents and heavy metals

- Mechlorethamine, melphalan, nitrosoureas, busulfan, chlorambucil
- Cyclophosphamide, ifosfamide, platinum analogs

- Mutagenic and carcinogenic (secondary AML)
- Associated with infertility (amenorrhea, azoospermia)
- Lung injury (High dose busulphan)
- Renal injury (with acquired Fanconi’s syndrome)
- Neurotoxicity, ototoxicity (irreversible if not diagnosed early)

Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007
Effects of chemo: Anthracyclines

Adriamycin, epirubicin, daunorubicin, idarubicin

- Late cardiotoxicity (free-radical damage of cellular nucleic acids, lipids and proteins):
  - Myocardial cell injury
  - Increased afterload
  - Left ventricular systolic dysfunction
  - Congestive heart failure

- The cumulative anthracycline dose seems to be the most important determinant of the incidence of cardiotoxicity

- Increased risk by chest irradiation, smoking, hypertension, diabetes, dyslipidemia, cardiotoxic agents


**Effects of chemo: cardiomyopathy**

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<tr>
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<td></td>
<td>in combination with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anthracycline</td>
</tr>
</tbody>
</table>

*Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007*
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Anthracycline</th>
<th>Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>&gt;550 mg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Yes (&gt;64 years)</td>
<td>Yes (&gt;50 years)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous heart disease</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Previous radiation therapy</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Concurrent chemotherapy</td>
<td>Yes</td>
<td>Yes^a</td>
</tr>
<tr>
<td>Hematopoietic cell transplantation</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Host susceptibility^5</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No^b</td>
</tr>
</tbody>
</table>

Blank cells in the table denote characteristics that are not risk factors or are inconclusive.

BMI, body mass index.

^a Especially with concurrent anthracycline use.

^b Small study suggests association in elderly women with diabetes.^6

Risk of Cardiotoxicity Associated With Chemotherapy

Pentheroudakis G and Pavlidis N Cancer Treat Rev 2007
Mortality due to cardiovascular event x6 after childhood cancer

2\textsuperscript{nd} cause of late toxicity

Cumulative rate of death
4122 survivors after 5 y
Treated between 1942 - 1986
Before age 15
France and U.K.

Tukenova, JCO, 2010
Main cardiotoxicities after cancer treatment in childhood and adolescence

- Cumulative rates at age 45 y

  - Ischemia: 5.3% vs. 0.9%
  - Clinical cardiac failure: 4.8% vs. 0.3%
  - Valvular disease: 1.5% vs. 0.1%
  - Arythmia: 1.3% vs. 0.4%

10.724 survivors more than 5 y after cancer treatment before 21 y in USA and Canada between 1970 and 1986 vs. 3159 brothers and sisters

Armstrong, JCO, 2013

12 may 2018
Congestive heart failure
Role of treatment

Mulrooney, BMJ, 2009
Cardiovascular disease after treatment for Hodgkin’s lymphoma: an analysis of nine collaborative EORTC-LYSA trials

6039 patients treated for Hodgkin in LYSA/EORTC trials between 1964 and 2004

Median age : 30.y   Median follow-up 9 y

Life situation questionnaire

1238 cardiac events in 703 patients

- congestive heart disease
- congestive heart failure
- arhythmia
- valvular disease

Van Nimwegen, JCO, 2015

Maralda, Lancet Oncol 2017

12 may 2018
Figure 2: Cumulative incidence of first cardiovascular disease by LSQ-responder status and by individual diagnoses

Figure 3: Estimated hazard ratio for cardiovascular events according to (A) mean heart radiation dose and (B) cumulative dose of anthracyclines in doxorubicin-equivalents
Management of treatment-induced cardiotoxicity

- Pretreatment assessment,
- Risk reduction,
- Surveillance and early treatment of cardiotoxicity during therapy,
- Post-treatment surveillance
Surveillance for cardiotoxicity

For whom?

For patients treated with anthracyclins or cardiac irradiation

How?

Cardiac Tripplex U/S

<table>
<thead>
<tr>
<th>Irradiation de l’aire cardiaque (dose max)</th>
<th>&lt; 20 Gy</th>
<th>≥ 20 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose cumulée d’anthracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 300 mg/m²</td>
<td>/ 5 ans</td>
<td>/ 3 ans</td>
</tr>
<tr>
<td>≥ 300 mg/m²</td>
<td>/ 3 ans</td>
<td>/ an</td>
</tr>
</tbody>
</table>
Role of early treatment with Enalapril

- 200 pts with LVEF < 45% after anthacycline treatment
- Treatment with enalapril and whenever possible carvedilol as soon as decrease of LVEF was detected
- 42% of patients were responders and had a decrease risk of cardiac events

Cardinale 2010
Stroke after irradiation of Willis circle arteries

- 3172 adults treated for a tumor before age 16 between 1942 and 1985 in France (FCCSS); median follow-up up 26 y

- 54 patients with a stroke
  - 38 ischemic
  - 16 hemorrhagic
  - 1 both
  - Cumulative incidence at age 50 = 6.8% (SIR = 6.9)

- Among 442 patients treated for a brain tumor
  - 26 stroke
  - Cumulative incidence at age 50 = 26.7%

Fayech, 2018
**Irradiation of Willis circle arteries: a major risk factor**

<table>
<thead>
<tr>
<th>Patients</th>
<th>All strokes (n=54)</th>
<th>Ischemic strokes (n=39)</th>
<th>Hemorrhagic strokes (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>RR* (95%CI)</td>
<td>n</td>
<td>RR* (95%CI)</td>
</tr>
<tr>
<td>970</td>
<td>4</td>
<td>1 (ref†)</td>
<td>2</td>
</tr>
<tr>
<td>1,267</td>
<td>12</td>
<td>1.5 (0.5-4.9)</td>
<td>6</td>
</tr>
<tr>
<td>300</td>
<td>9</td>
<td>5.0 (1.4-17.4)</td>
<td>7</td>
</tr>
<tr>
<td>386</td>
<td>13</td>
<td>7.9 (2.5-24.6)</td>
<td>13</td>
</tr>
<tr>
<td>249</td>
<td>16</td>
<td>15.7 (4.9-50.2)</td>
<td>11</td>
</tr>
</tbody>
</table>

Average radiation dose to the cerebral arteries (Gy)

- **No radiotherapy**
  - 970 patients: 4 events
  - 1 event (ref†)
  - 1 event (ref†)
  - 2 events

- **< 1 Gy**
  - 1,267 patients: 12 events
  - 1.5 (0.5-4.9) events
  - 6 events (1.5 (0.3-7.5))
  - 6 events (1.5 (0.3-8.1))

- **1 < 10 Gy**
  - 300 patients: 9 events
  - 5.0 (1.4-17.4) events
  - 7 events (6.6 (1.3-34.7))
  - 3 events (2.0 (0.3-12.6))

- **10 < 40 Gy**
  - 386 patients: 13 events
  - 7.9 (2.5-24.6) events
  - 13 events (14.5 (3.2-65.2))
  - 0 events

- **40 and + Gy**
  - 249 patients: 16 events
  - 15.7 (4.9-50.2) events
  - 11 events (19.0 (3.9-92.2))
  - 5 events (12.6 (2.1-78.0))

Fayech, 2018
Stroke after Hodgkin lymphoma

- 2251 HL treated before age 51 between 1965 and 1995
- Median follow-up 17.8 y
- 96 cerebrovascular diseases (55 strokes, 31 TIA, 10 both)
  - Carotid 76%
  - Vertebro-basilar 13%
  - Both 7%
- Median age at stroke 51 y
- Outcome
  - 9 died
  - 2 severe symptoms
  - 29 mild symptoms
  - 48 complete recovery
- Radiation to the neck and mediastinum was an independent risk factor (HR = 2.5, 95%CI 1.1 - 5.6) vs without radiotherapy

De Bruyne, JNCI, 2009
PREVENTION of CARDIOVASCULAR COMPLICATIONS

■ AVOID RISK FACTORS

■ Tobacco

■ Overweight

■ Hypercholesterolemia

■ Diabetes

■ Hypertension

■ PHYSICAL ACTIVITY
Suggested follow-up

- For all patients with cerebral radiotherapy
  Brain MRI angiography every 5 years

- Irradiation cervical > 20 Gy:
  Ultrasonography of carotid vessels every 3-5 years
Effects of chemo: Antimetabolites and Topo-inhibitors

1. Antimetabolites: Methotrexate, mercaptopurine, cytarabine, gemcitabine
2. Topo-inhibitors: etoposide, irinotecan, topotecan
3. Anticancer Antibiotics: bleomycin

- Osteopenia (High-dose methotrexate)
- Secondary 11q23 AML (Etoposide >2 g/m², 5-10% probability)
- Lung injury, pulmonary fibrosis, respiratory failure (Bleomycin >300-360 IU, <2% of adolescents)
Effects of chemo: steroids

- Hyperglycemia ➔ insuline resistance ➔ diabetes
- Hypertension
- Skin changes , hypertrichosis
- Myopathy, muscular atrophy
- Immunosuppression,
- Osteopenia, osteoporosis, bone necrosis (aseptal femoral head necrosis)
- Mood disturbances (agitation, depression, anxiety)

*Pentheroudakis G and Pavlidis N* Cancer Treat Rev 2007
Effects of treatment: Osteopenia

- Multifactorial, may lead to clinically significant osteoporosis in adult life:
  - Irradiation
  - Chemotherapy-associated hypogonadism
  - Pituitary dysfunction (Cranial irradiation)
  - Hypothyroidism
  - Steroid-induced bone resorption
  - Renal calciuresis and vitamin D deficiency
  - Poor diet and nutrition

Bhatia S et al. JCO 2003
Effects from irradiation:

**Cranial/Neck/Chest Rx**

- Reduced intellectual capacity-cognition is rare
- Subclinical verbal, non-verbal, visual-spatial and attention-concentration deficits
- Neuroendocrine dysfunction (GH, GnRH, TSH, ACTH low. Prolactin high)
- Hypothyroidism
- Cardiopulmonary disease
- Lung/breast/thyroid cancer

Effects from irradiation:

**Abdomino-pelvic Rx**

- Chronic enteritis
- Chronic malnutrition
- Intestinal fibrosis (5%)
- Tubular and glomerular dysfunction
- Hypertension (8%)
- Renal impairment (11%)
- Calciuresis-osteopenia
- Bladder fibrosis (rare)
- Gastric/Colorectal/Pancreatic/Bladder cancer

“Take home” messages

- Surgery, chemotherapy and irradiation can be associated with substantial toxicity from many target organs, depending on the timing, intensity and combination of regimens.

- These toxicities are of particular concern for AYA because of their young age and very long life expectancy.

- Care of AYA with cancer should be always directed in maximizing efficacy and cure potential and at the same time minimizing short and long term toxicities that can significantly impair young patients’ quality of life.
Thank you for your attention!