Cancer in Adolescents and Young Adults

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Outline of the presentation

- Epidemiology
- Risk factors
- Management and care
- Late toxicities
- Clinical Research
AYA Cancer: “No man’s land?”

- Unique disease constellation with distinct epidemiological, clinical and biological characteristics that resemble neither to childhood cancer nor cancer in older adults.

- The lower incidence of AYA-onset cancer as compared to older adults, along with the paucity of cancer clinical trials in this age group, have hampered the elucidation of the molecular biology of these tumours, which is the key to the optimal therapeutic approach and improvements in clinical outcomes.
AYA are usually considered as the older patients in pediatric oncology, or hematology practice and the younger patients in adult practice.

At present, there are no universally accepted limits that define the age range because the interface between adult and children’s services is different in different healthcare systems.


Teenage years are between 13 and 19 years of age, inclusive.

Older patients, 20-39 years of age, are generally considered as “young adults”.

1 Erikson, E. Identity: Youth and Crisis New York Norton 1968
Epidemiology: Incidence

- Cancers in AYA are rare.

- Annual rate: ~200-300 cases per million persons.\(^1\)

- 50% higher annual incidence comparing adolescents to younger children, and 50% higher again comparing adolescents to Young Adults.\(^1\)

- Rising cancer incidence: 0.9% per year.\(^2\)

  - The increase is mainly attributed to juvenile melanoma (5% increase), non-Hodgkin lymphomas (NHL, 2% increase) and germ-cell tumours (2% increase).\(^2\)

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\(^1\) Ries LAG et al. SEER Cancer Statistics Review, NCI 2001
Graph: Bleyer A et al. Oncologist 2006;11(6):590-601
Incidence according to age

Bleyer A et al. Oncologist 2006;11(6):590-601
No diseases begin or end at age 18 years

But: In many countries the age of 18 defines the beginning of adulthood, with important biological (physical and gonadal maturation) and clinical (legal independence and ability to sign consent form, insurance coverage for treatment in adult services) implications.

1 Sallan S. Hematology 2006;128-132
Graphs: Cancer Epidemiology in AYA, SEER
Distribution of cancer types in AYA

Pritchard-Jones K et al. Lancet Oncol 2013;14(3):e95-103
Epidemiology: Not an adult, not a child

- Hodgkin’s disease (HD) and Germ-cell tumours are 3-6 times higher in adolescents than in the pediatric population.

- Epithelial carcinomas, nasopharyngeal carcinomas, thyroid cancer and melanomas are seen in AYA.

- NHL and CNS tumours are almost as common in adolescents as in childhood.

- ALL is less frequent, whereas osteosarcoma is most frequent in AYA.

- Embryonal Rhabdomyosarcoma, Wilms Tumours, and neuroblastomas are rarely seen true “pediatric type” tumours occurring in AYA.

- Epithelial tumours (breast, colon, cervical etc) are seen in adolescents but significantly more often in young adults.

Bleyer A et al. Oncologist 2006;11(6):590-601
Epidemiology and sex

More common in males:
- ALL
- NHL
- Ewing/PNET
- Osteosarcomas
- CNS

More common in females:
- Thyroid cancer
- Melanoma
- Hodgkin’s disease

Slightly higher incidence in males

Bleyer A et al. Oncologist 2006;11(6):590-601
Risk factors: Genetic

- The vast majority of cancers in AYA are sporadic events of unknown etiology.
- Genetic syndromes associated with increased incidence of AYA cancer represent less than 10% of all cases but include:
  - Neurofibromatosis (NF1 and NF2)
  - Li-Fraumeni syndrome (TP53)
  - Xeroderma pigmentosum (XP)
  - Ataxia-telangiectasia (ATM)
  - Fanconi pancytopenia
  - Hereditary dysplastic nevus syndrome
  - Turner, Beckwith-Wiedemann, Bloom and Gorlin’s syndromes
  - Multiple Endocrine Neoplasia syndromes (MEN)
  - BRCA1/BRCA2 tumor suppressor gene mutations
  - Familial Adenomatous Polyposis and Lynch syndromes
- Those managing AYA cancers need expertise in taking a full family history.
Risk factors: Environmental

In rare cases environmental factors have been observed in the pathogenesis of AYA cancer:

- Clear-cell adenocarcinoma of the vagina or cervix (Maternal exposure to diethylstilbestrol during pregnancy)
- Liver tumours (Congenital exposure to HBV/HCV)
- Cervical Cancer (HPV)
- Kaposi Sarcoma (HIV)
- HL and Burkitt lymphoma (EBV)
- Second primary tumours (childhood exposure to chemo-radiation)
- Juvenile melanoma (UV sunlight exposure)
**Classification**

- AYA tumours are not best classified using an adult cancer classification system which is tumour primary-site specific. In contrast, they may be classified by a pathology-driven approach.

<table>
<thead>
<tr>
<th>Tumour group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Leukaemias</td>
</tr>
<tr>
<td>Group 2</td>
<td>Lymphomas</td>
</tr>
<tr>
<td>Group 3</td>
<td>CNS tumours</td>
</tr>
<tr>
<td>Group 4</td>
<td>Bone tumours</td>
</tr>
<tr>
<td>Group 5</td>
<td>Soft tissue sarcomas</td>
</tr>
<tr>
<td>Group 6</td>
<td>Germ cell tumours</td>
</tr>
<tr>
<td>Group 7</td>
<td>Melanoma and skin carcinoma</td>
</tr>
<tr>
<td>Group 8</td>
<td>Carcinomas (except of skin)</td>
</tr>
<tr>
<td>Group 9</td>
<td>Miscellaneous specified neoplasms (including embryonal paediatric tumours)</td>
</tr>
<tr>
<td>Group 10</td>
<td>Unspecified malignant neoplasms</td>
</tr>
</tbody>
</table>

Birch JM *et al.* Br J Cancer 2002;87(11):1267-74
AYA tend to consider themselves as “unaffected” by serious disease, such as cancer.

Professionals and patients may underestimate symptoms that should be stimulating investigation (e.g. severe fatigue, headache, enlarged lymph nodes, weight loss etc).

Demanding education or work-place obligations may lead AYA to neglect health issues.

Reluctant to report symptoms or signs related to reproductive system, and may longer be a parent to advocate for them (e.g. amenorrhea, testicular mass).
Nowadays, approximately 3 out of 4 adolescents with cancer achieve long-term survival.

5-year survival rates for the most common tumour types (CNS tumours, NHL, ALL, HL, germ-cell tumours) range from 45% to 90%.

The curative aim necessitates that many treatments ought to be given in a “state of the art” fashion within international study protocols requiring:

- Combined modality treatment
- Aggressive surgery when feasible
- High-dose radiotherapy when indicated
- Dose-dense, or high-dose chemotherapy with autologous marrow/stem-cell rescue in defined indications or within trials
- Avoidance of unnecessary treatment delays or dose reductions

Management and care: Expertise

- Adolescents have to be treated by skilled personnel under an appropriate infrastructure. ¹

- Evidence from retrospective and cohort studies indicate that the outcome is superior when treatment is given in a reference cancer centre. ²

- Survival seems to correlate with the number of adolescents with malignancy seen annually in each center. ²

- The National Institute for Health and Clinical Excellence (UK) and the National Cancer Institute (US) have commissioned recommendations for the organization of optimal care of young people with cancer. ³,⁴

⁴ AYA progress review group. US Department of Health and Human Services 2006
Different therapeutic approaches may lead to different outcomes

- **Protocole FRALLE 93**
  - Pediatric protocol (<20 years)
  - Start June 1993
  - 77 adolescents (15-20 years)

- **Protocole LALA 94**
  - Adult Protocol (15-60 years)
  - Start October 1994
  - 100 adolescents

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5 year - EFS

- FRALLE 93: 67% (± 13)
- LALA 94: 41% (± 14)

P<0.0001

Management: Psychosocial issues

- Challenges encountered by the AYA with cancer:
  - Loss of independence
  - Interruption of education or employment
  - Changes in the physical/ body appearance
  - Impact on sexual maturation
  - Fertility and reproduction issues
  - Family conflicts
  - Isolation from peers (The “stigma” of cancer)
  - Struggle for reconciliation with diagnosis
  - Retaining the hope for cure

Balancing Schoolwork and Hospital Stays

When Cancer Keeps You Home
Management: Psychosocial issues

- Changes of the physical/body image perception, when confidence in personal appearance is so central to AYA self esteem and social integration:
  - Mutilating surgery/disfigurement/loss of function
  - Radiotherapy-induced skin changes
  - Alopecia
  - Acne
  - Weight gain or weight loss
  - Amenorrhea/infertility
  - Stunted growth
  - Delay of puberty
  - Disruption of normal sexual function

Management: Psychosocial Support

- Skilled, individualized psychological support by personnel with specific communication skills (e.g. timing of key discussions, use of humour).
- Communication should offer and expect to encompass family, girl/boyfriend, friends, educational and work environment for different issues at different times, with the AYA at the centre. ¹
- Support by physiotherapists, dentists, make-up specialists and plastic surgeons.
- Support by social workers ensuring smooth re-incorporation into educational, professional and social activities. ²
- Peer group support should continue during treatment:
  - AYA patients can benefit from being managed together so they are ‘all in the same boat’ ¹

Management: Late Toxicities

- Defined as the late effects of antineoplastic treatment occurring more than six months 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.

Late Toxicities by Surgery

- 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 with recent advances in surgery, such as fertility-preservation surgery, and limb-sparing surgery with modern endoprostheses.

Late toxicities after ionizing irradiation

Table 1  Approximate TD_{5/5} and TD_{50/5} radiation doses

<table>
<thead>
<tr>
<th>Organ</th>
<th>Late effects</th>
<th>TD_{5/5} (\text{Gy})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis</td>
<td>Sterility</td>
<td>1–3</td>
</tr>
<tr>
<td>Ovary</td>
<td>Sterility</td>
<td>6–10</td>
</tr>
<tr>
<td>Lens</td>
<td>Cataract</td>
<td>6–12</td>
</tr>
<tr>
<td>Kidney</td>
<td>Renal sclerosis</td>
<td>23–30</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Necrosis–fibrosis</td>
<td>20–40</td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonitis–fibrosis</td>
<td>23–30</td>
</tr>
<tr>
<td>Skin</td>
<td>Atrophy–fibrosis</td>
<td>30–40</td>
</tr>
<tr>
<td>Liver</td>
<td>Radiation hepatitis</td>
<td>35–40</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Hypoplasia–aplasia</td>
<td>35–50</td>
</tr>
<tr>
<td>Heart</td>
<td>Pericarditis, cardiomyopathy</td>
<td>43–50</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Necrosis, fibrosis, ulceration</td>
<td>42–55</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Vasculitis, necrosis–fibrosis</td>
<td>50–60</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Myelopathy</td>
<td>45–60</td>
</tr>
<tr>
<td>Brain</td>
<td>Encephalopathy</td>
<td>45–65</td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>Neuropathy</td>
<td>65–75</td>
</tr>
<tr>
<td>Mucosae</td>
<td>Necrosis–fibrosis, ulceration</td>
<td>55–75</td>
</tr>
<tr>
<td>Bone</td>
<td>Necrosis, fracture</td>
<td>60–75</td>
</tr>
<tr>
<td>Muscle</td>
<td>Oedema, necrosis, fibrosis</td>
<td>60–75</td>
</tr>
</tbody>
</table>

### Cranial/Neck/Chest Rx
- Reduced intellectual capacity is rare
- Subclinical verbal, non-verbal, visual-spatial and attention-concentration deficits
- Neuroendocrine dysfunction (GH, GnRH, TSH, ACTH low Prolactin high)
- Future Metabolic syndrome?
- Hypothyroidism
- Cardiopulmonary disease
- Lung/breast/thyroid cancer

### Abdominopelvic 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

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Late toxicities after 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>Mitoxantrone</td>
<td>Pulmonary toxicity</td>
<td>6500 in a few days</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Cardiomyopathy</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>70 in monotherapy, 30 in combination with anthracycline</td>
<td></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/KB/ in a few days</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Pulmonary 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.

Late Toxicities by Chemotherapy

- Alkylating agents and heavy metals:
  - Mechloretamine, melphalan, nitrosoureas, busulfan, chlorambucil
  - Cyclophosphamide, ifosfamide, platinum analogs

- Mutagenic and carcinogenic (secondary AML)

- Lung injury (High dose busulphane)

- Renal injury (with acquired Fanconi’s syndrome)

- Neurotoxicity, ototoxicity (usually irreversible)

Late Toxicities by Chemotherapy

- **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.
Late Toxicities by Chemotherapy

- **Antimetabolites**: Methotrexate, mercaptopurine, cytarabine, gemcitabine and other drugs (etoposide, bleomycin, steroids).
- 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).
- Myopathy, immunosuppression, diabetes, hypertension, bone necrosis, mood disturbances (steroids).

Late Toxicities: Osteopenia

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

Late Toxicities: Infertility

- Frequency, degree and duration of infertility depend on the dose and type of therapy administered, the patient’s age and gonadal reserve.
- Testicular, ovarian and hypothalamic/pituitary irradiation, as well as chemotherapy with alkylating agents are major risk factors.
- Fertility-sparing surgery or irradiation plan should be implemented when feasible and safe.
- Post-pubertal sperm banking, female oocyte harvesting, or embryo banking and cryopreservation should be discussed prior to treatment initiation.

Metzger ML et al. J Clin Oncol 2013;31(9):1239-47
How frequent are second malignancies in adolescents and young adults who survived a first cancer?

- In 13,581 cured AYA, second cancer in 3.2% within 20 years (HR=6.4) \(^1\)

- In 31,000 cured AYA, second cancer in 3.5% within 25 years (HR=3.6) \(^2\)

\(^1\) Neglia J \textit{et al.} J Natl Cancer Inst 2001;93(8):618-29

Late Toxicities: Second Cancer

- Which are the tumours most frequently associated with second malignancies?
  - Familial Retinoblastoma
  - Hodgkin’s Lymphoma
  - Soft tissue sarcomas

- Which are the second malignancies?
  - Acute Myelogenous Leucemia (AML)
  - Myelodysplastic syndromes
  - Epithelial tumours (“adult” type)- e.g. after germ cell tumour chemotherapy

Late Toxicities: Second Cancer

Special correlations between first and second cancers

<table>
<thead>
<tr>
<th>PRIMARY CANCERS</th>
<th>SECOND CANCERS</th>
<th>LATENCY (median in years)</th>
<th>RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL; HD; Bone tumors</td>
<td>MDS/AML</td>
<td>3-5</td>
<td>Alkylating agents Topoisomerase II inhibitors</td>
</tr>
<tr>
<td>ALL; HD</td>
<td>CNS tumors</td>
<td>8-10</td>
<td>CNS irradiation</td>
</tr>
<tr>
<td>Retinoblastoma; EWS; STS; ALL</td>
<td>Bone tumors and thyroid cancer</td>
<td>8-10</td>
<td>Irradiation, alkylating agents</td>
</tr>
<tr>
<td>Retinoblastoma; EWS; bone tumors; ALL</td>
<td>STS</td>
<td>10-12</td>
<td>Irradiation, anthracyclins</td>
</tr>
<tr>
<td>HD; STS; bone tumors; ALL; NHL</td>
<td>Breast Cancer</td>
<td>15-20</td>
<td>Irradiationon Female gender</td>
</tr>
</tbody>
</table>

Courtesy of G Mountzios and G Pentheroudakis
Prognosis

- Overall 5-year survival for adolescents with cancer: 87% (EUROCARE).

- Best results:
  - Hodgkin’s lymphoma
  - Thyroid Cancer
  - Germ-cell tumours

- Worse prognosis:
  - AML, ALL
  - NHL
  - Sarcomas

5-year survival of 30,187 patients with cancer in Europe treated between 1994 and 2002

- 83 registries in 23 European countries
- 5 year-OS: 87%

Why?

Survival modifications over time in AYA

- Survival improvement, especially in lymphoma.
- No survival improvement in osteosarcoma.


<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid leukaemias</td>
<td>0.91</td>
</tr>
<tr>
<td>Acute myeloid leukaemias</td>
<td>0.81</td>
</tr>
<tr>
<td>Hodgkin lymphomas</td>
<td>0.87</td>
</tr>
<tr>
<td>Non-Hodgkin lymphomas</td>
<td>0.70</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>0.99</td>
</tr>
<tr>
<td>Brain</td>
<td>0.89</td>
</tr>
<tr>
<td>Astrocytomomas</td>
<td>0.99</td>
</tr>
<tr>
<td>Bone</td>
<td>0.99</td>
</tr>
<tr>
<td>Osteosarcomas</td>
<td>1.25</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Reasons?

- Pathway to diagnosis?

- Poor trial recruitment, hence disappointing improvements in outcome over time:
  - Not enough of a contribution to large-scale trials

- Adherence with treatment:
  - ‘When non-adherence rates are examined “…adolescents are consistently less adherent than younger or older patients with cancer, even when treated on similar protocols for similar diseases”’
  - May be improved by: specific AYA communication, support, flexibility and peer-group support

- Biology

- Less care entitlement in private-insurance healthcare systems.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>≤12 years old</th>
<th>&gt;12 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma</td>
<td>2.6 months</td>
<td>3.8</td>
</tr>
<tr>
<td>Ewing Sarcoma</td>
<td>3.7</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Biology - AYA germ cell tumours

Not the same diseases as in childhood or adulthood

Principal components cluster analysis of gene expression in germ cell tumours in children and adults with malignant GCTs

## Table 1. Summary of the Pharmacology Studies Published in Adolescents

<table>
<thead>
<tr>
<th>Drug and Study</th>
<th>No. of Patients</th>
<th>Age Range (years)</th>
<th>Sex</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide</td>
<td>39</td>
<td>0.7-21.9</td>
<td>M 20</td>
<td>F 19</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>214</td>
<td>1.0-18.8</td>
<td>M 115</td>
<td>F 99</td>
</tr>
<tr>
<td>Topotecan</td>
<td>162</td>
<td>0.04-22</td>
<td>M 110</td>
<td>F 52</td>
</tr>
<tr>
<td>Vincristine</td>
<td>54</td>
<td>0.2-18</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vincristine</td>
<td>98</td>
<td>1.3-17.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Imatinib</td>
<td>26</td>
<td>7.0-24</td>
<td>M 17</td>
<td>F 9</td>
</tr>
<tr>
<td>Imatinib</td>
<td>15</td>
<td>6.0-22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Etoposide</td>
<td>29</td>
<td>1.58-23.9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Etoposide</td>
<td>16</td>
<td>0.3-22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Etoposide</td>
<td>31</td>
<td>0.8-23.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Etoposide</td>
<td>18</td>
<td>1.1-17</td>
<td>M 10</td>
<td>F 8</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>134</td>
<td>0.33-18.5</td>
<td>M 76</td>
<td>F 58</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>122</td>
<td>0.26-15</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>40</td>
<td>0.5-17</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>31</td>
<td>1.0-20</td>
<td>M 18</td>
<td>F 13</td>
</tr>
<tr>
<td>Busulfan</td>
<td>27</td>
<td>1.3-50</td>
<td>M 10</td>
<td>F 17</td>
</tr>
<tr>
<td>Busulfan</td>
<td>25</td>
<td>0.5-54</td>
<td>M 15</td>
<td>F 10</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; Cl, clearance; BW, body weight; AUC, area under the curve; BSA, body-surface area.

Clinical Research: Drawbacks and common misperceptions

- In USA, only 10% of adolescents are entered to clinical trials sponsored by NCI - not enough patients to make progress.
  - Very little biological data being collected
- In Europe, many adolescents treated in pediatric institutions are entered into co-operative group trials but the entry rate remains low for patients treated outside of established networks.
- Illogical exclusion criteria regarding age eligibility are commonly seen in clinical trials:
  - Diseases which cross the pediatric-adult spectrum and yet the trial age-of-entry criteria represent professional boundaries (0-18 or 18-70), not patient needs
- Misperception of poor adolescent compliance to complex protocols.
  - Centres with higher AYA caseloads may enrol a higher proportion of AYA into clinical trials
- False belief that a trial is not needed because of an “excellent” prognosis.

Clinical trial participation by age group

Participation of children, adolescents and young adults with cancer in clinical trials and cooperative treatment protocols in the USA.
White area: neither protocol nor trial.
Mid-shading: only cooperative group protocol.
Darkest shading: entered into both protocol and trial.

SEER data, US National registry 2007
Working groups in the US and Europe have begun addressing the problem.

Retrospective analyses of AYA cancer data in published trials are ongoing.

Organization of clinical trials for tumours affecting adolescents jointly by pediatric and adult oncology cooperative groups.

Banking of biological tissue for translational research.

In the European level, to manage AYA cancer, cooperation between adult and pediatric oncology is mandatory.
“Take home” messages

- Unique patient population: not a child, not an adult.
- Unique range of affecting malignancies: midway between pediatric and adult tumour epidemiology.
- Unique support for patient and family needed.
- Expertise needed for state of the art management of the AYA.
- Cure is the goal.
- Avoidance of undertreatment.
- Avoidance of overtreatment and debilitating late toxicities.
- Multidisciplinary management in reference centers mandatory.
- Psycho-social support required.
- Long-term follow up necessary, optimal model to be defined.
- Prognosis excellent for some, however improvement in several areas is needed (and is lagging behind that seen in pediatric and adult tumours).
- Clinical research and accrual in clinical trials has been neglected.
AYA deserve the best of both worlds!!
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