Cancer in adolescents and Young Adults

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Gustave Roussy Cancer Center
Villejuif, France
Cancer in TYA

A rare disease in patients in transition between childhood and adulthood

15-19 y

15-25 y

15-39 y
Medical challenges in AYA

- A unique spectrum of rare cancer types
- Long time to referral
- Multiple therapeutic options: need for a double expertise: site and age specific
- Distinct tumor biology in this age group
- Low rate of inclusion into trials
- Specific psycho-social needs
- Fertility preservation and long term follow-up
Estimated TYA (15-24 y) population in European Union: 58 million

14,000 new cancer cases/year in TYA in Europe

Cancer is the second cause of death in TYA
A unique spectrum of cancer types

17th ESO-ESMO Masterclass in Clinical Oncology
A unique spectrum of cancer types

Need for collaboration

Children  TYA  Adults

Age (y)
Lymphomas

Hodgkin

LNH

N. Gaspar
Bone tumors

Osteosarcoma

Ewing

Chondrosarcoma

Incidence per Year per Million

Age at Diagnosis (Years)
Soft tissue sarcomas

RMS

Non RMS sarcomas

Figure 7.7: Incidence of Rhabdomyosarcoma by Gender, SEER 1975-1999

Figure 7.8: Incidence of Fibrosarcoma, Neurofibrosarcoma, and Other Fibromatous Neoplasms by Gender, SEER 1975-1999
Gonadal tumors

Figure 13.4: Incidence of Testicular Cancer in Males, All Ages SEER 1975-2000

Figure 14.10: Incidence of Ovarian Cancer, Excluding Borderline Histology, SEER 1975-1999
Carcinomas

**Breast**

![Incidence of Breast Cancer in Females, SEER 1975-2000]

**Colon**

![Incidence of Colorectal Carcinoma by Gender, SEER 1975-2000]

**Thyroid**

![Incidence of Differentiated (Papillary and Follicular) Thyroid Cancer, SEER 1975-2000]

Genetic predisposition syndromes

N. Gaspar
Melanomas

Prevention
Medical challenges in AYA

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• Aspecific symptoms

• Insuffisant awareness that cancer may happen in this age group

• Diagnostic pathway often complex with multiple consultations and consequent delay

• Median delay for diagnosis : 8 weeks for TYA and weeks in young adults in France

Étude EXECADO, E desandes France 2006-2007
# Delays in diagnosis and treatment in French TYA

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
<th>15-19 y Time to diagnosis (w) Median (25-75%)</th>
<th>20-24 y Time to diagnosis (w) Median (25-75%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>92 (9%)</td>
<td>1.7 (1.1-5.2)</td>
<td>3 (1.3-6.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>233 (23%)</td>
<td>7.1 (3.7-15.7)</td>
<td>10.9 (4.1-21.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>111 (11%)</td>
<td>12 (4.7-29.5)</td>
<td>9.7 (3.9-27.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Bone tumors</td>
<td>48 (5%)</td>
<td>10.1 (5.8-27.4)</td>
<td>21.4 (3-54)</td>
<td>0.42</td>
</tr>
<tr>
<td>Soft Tissue sarcoma</td>
<td>43 (4%)</td>
<td>15.4 (5.4-34.7)</td>
<td>48.7 (21-15.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>133 (13%)</td>
<td>6.7 (2.1-12.8)</td>
<td>5.8 (21-85.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Carcinomas /melanomas</td>
<td>318 (32%)</td>
<td>10 (1.6-24.3)</td>
<td>13.9 (5-27.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Other tumors</td>
<td>15 (12%)</td>
<td>14.4 (13.7-15.1)</td>
<td>10.4 (8.1-40.4)</td>
<td>0.55</td>
</tr>
<tr>
<td>All tumors</td>
<td>993</td>
<td>7.7 (2.6-21.3)</td>
<td>9.9 (3.7-22.6)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Desandes in press 2018
Timely referral
Medical challenges in AYA

- A unique spectrum of rare cancer types requiring expertise
- Long time to referral
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Survival Improvement Gap in 5-year relative survival 1975-1997 (invasive cancer)


From SEER data
5-year relative survival estimates by age at diagnosis and by sex, for all cancers combined, diagnosed in Europe in 2000–07

5-y OS 79% (78.9–79.3) in TYA

5-y OS 76% (95% CI 75–77) in children
Cancer in TYA in Europe 2000-2007
5-y survival

Colon
Breast
Melanoma
GCT
STS
Ewing
osteosarcoma
CNS
NHL
Hodgkin
AML
ALL

20-39y  15-19-y  0-14y

0  10  20  30  40  50  60  70  80  90  100

Trama 2016 Lancet Oncol

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Trends in 5-year OS in 5 cancer categories 1999-2007

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ALL: outcome better with pediatric protocols
ALL in teenagers: outcome according to the site of treatment

EFS (%)

- Pédiatrie
- Adulše

P = 0.05

OS (%)

- Pédiatrie
- Adulše

P = 0.04

N. Gaspar
Hodgkin lymphoma: cost of cure

**Planned Cumulative Exposure**

<table>
<thead>
<tr>
<th>Agent</th>
<th>ABVD: 6-8 Cycles, 24-32 Weeks</th>
<th>Stanford V: 12 Weeks</th>
<th>ABVE-PC: 4 Cycles, 12 Weeks</th>
<th>DECA: 2 Cycles, 6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin, mg/m²</td>
<td>300-400</td>
<td>150</td>
<td>200</td>
<td>—</td>
</tr>
<tr>
<td>Bleomycin, U/m²</td>
<td>120-180</td>
<td>30</td>
<td>60</td>
<td>—</td>
</tr>
<tr>
<td>Vinblastine, mg/m²</td>
<td>72-96</td>
<td>36</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Vincristine, mg/m²</td>
<td>8.4</td>
<td>11.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dacarbazine, g/m²</td>
<td>4.5-6.0 g/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cyclophosphamide, g/m²</td>
<td>—</td>
<td>—</td>
<td>3.2</td>
<td>—</td>
</tr>
<tr>
<td>Mechlorethamine, mg/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Etoposide, mg/m²</td>
<td>—</td>
<td>360</td>
<td>1500</td>
<td>400</td>
</tr>
<tr>
<td>Prednisone, mg/m²</td>
<td>—</td>
<td>—</td>
<td>1120</td>
<td>—</td>
</tr>
<tr>
<td>Dexamethasone, mg/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>Cytarabine, g/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12</td>
</tr>
<tr>
<td>Cisplatin, mg/m²</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>180</td>
</tr>
</tbody>
</table>

Abbreviations: ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; ABVE-PC, doxorubicin (Adriamycin), bleomycin, vinblastine, etoposide, prednisone, and cyclophosphamide; DECA, dexamethasone, etoposide, cisplatin, and cytarabine; Stanford V, doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, and prednisone.

*The cumulative dose does not reflect taper in weeks 10 through 12.*
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- Specific psycho-social needs
- Fertility preservation and long term follow-up
Frequency of recurrent cytogenetic abnormalities in B-ALL with age

Tricoli, Cancer 2016
Complexity Index in Sarcoma

Genomic Index prognostic signatures

Children

Adults

Molecular biology

AJA ????

CINSARC

GI

Meta

N. Gaspar

Courtoisie de F. Chibon
Molecular profile according to age

Médulloblastoma

- Infant-like SHH (PTCH1, SUFU)
- Adult-like SHH (PTCH1, SMO)
- Young adult-like SHH (PTCH1, TP53)

Kool et al. Cancer cell 2014
Need to increase tumor banking

Figure 15.7: Number of Tumor Bank Specimens Compared with Incidence of Cancer by Age
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Low inclusion rates in clinical trials


Also reported in
- Australia
- Canada
- Italy
- UK
- France

Ferrari and Bleyer, 2007
TYA Inclusion rate higher in diseases where JOINT paediatric/adult trials are available

Highest rate of teenage accrual
But still not sufficient in young adults
Fern et al. TLO 2014
Low rate of inclusion in clinical trials

- Only few common trials for adult and children with the same tumor types
  - The best are bone tumors...

- Age limit of inclusion in most clinical trials: 18 y

  « No diseases begin or end at age 18 years »

*Sallan, Hematology 2006*
Delay of drug access in common diseases e.g. Hodgkin disease

**Brentuximab**

Adult Phase I trial ≥ 18 years
Relapsed or refractory CD30 positive HL
NCT00430846
Published Nov 2011

Approved for adult relapsed or refractory HL (2012)

Successful trial of BV + Chemotherapy in Adults
Stage II-IV HIV- HL, first line TT
NCT01771107
March 2013- 2017

Approved by FDA for front line TT of high risk HL
2018

**Nivolumab**

Paediatric Phase-I/II trial of BV < 18 years for R/R HL
NCT01492088
Randomized Phase 3 Study of BV for Newly Diagnosed High-Risk HL in Children and Young Adults (<21 y)
How to improve access to new drugs?

FAIR Trials working group: Proposal

Joint Adolescent – Adult Early Phase Clinical Trials to Improve Access to New Drugs for Adolescents with Cancer: Proposals from the Multi-stakeholder Platform – ACCELERATE


on behalf of Members of Working Group 1 of the Paediatric Platform of ACCELERATE


Published: 16 January 2018

Free Access !!!
Thanks to ITCC and SIOPE

https://doi.org/10.1093/annonc/mdy002
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- Fertility preservation and long term follow-up
Unique complex psycho-social needs

Many challenges
- Loss of control and independence
- Self-image dissatisfaction
- Difficulty establishing relationships,
- Sexuality self-confidence
- Limitation of «normal» activities….

Communication skills required to improve compliance and treatment adherence;

Adopt a family-centred approach

Need for a specific environment providing
- respects AYA privacy and dignit
- peer-group support,
- psychologists,
- education and vocational mentors,
- specialists nurses,
- social workers,
- activity coordinators

Several models:
- TYA units
- Dedicated teams in adult and pediatric centers
Compliance:

- Non compliance is a major issue in adolescent oncology
- Crucial problem with orally administered anticancer therapy
- Prevention:
  - Fair and complete information
  - Good interaction between the adolescents and health providers
  - Early recognition **at the time of diagnosis** those patients at risk of non-compliance so that preventive measures can be instituted
Specific needs of AYA

- Professional team trained to interact with AYA familiar with communication issues specific to the emotional fragility of this age group able to give them a clear, appropriate and comprehensive information at all stages and a level of control on the decision making system.

- Environment designed for young people with age appropriate facilities.

- The possibility to keep the social life as normal as possible ~ trying to keep links with family members and their peers.

- Contact with peers experiencing the same problems.

- Facilitation of education.

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Excess of morbidity and mortality

**Excess of morbidity**
15-29 y, 1975-2005

**Excess of mortality**

At 5 y HR 1.76
At 20 y HR 1.36

Youn, Cancer, 2014

Robison, Nature
review cancer, 2014
Long term side effects in survivors

Less cardiotoxicity of anthracyclines in adolescents/children

<table>
<thead>
<tr>
<th>Gender</th>
<th>Congestive heart failure</th>
<th>Myocardial infarction</th>
<th>Pericardial disease</th>
<th>Vascular abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P value</td>
<td>Hazard ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Male</td>
<td>1.0†</td>
<td>—</td>
<td>1.0†</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>1.4 (1.1 to 1.9)</td>
<td>0.018</td>
<td>0.6 (0.4 to 0.9)</td>
<td>0.014</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 years</td>
<td>3.9 (2.1 to 7.3)</td>
<td>&lt;0.001</td>
<td>1.0 (0.4 to 3.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>5-9 years</td>
<td>2.3 (1.3 to 4.0)</td>
<td>0.004</td>
<td>1.9 (0.9 to 4.0)</td>
<td>0.090</td>
</tr>
<tr>
<td>10-14 years</td>
<td>1.2 (0.8 to 1.9)</td>
<td>0.37</td>
<td>0.8 (0.4 to 1.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>15-20 years</td>
<td>1.0†</td>
<td>—</td>
<td>1.0†</td>
<td>—</td>
</tr>
</tbody>
</table>

Less ototoxicity of cisplatinum in ado vs children

Relative risk of deafness in 74 osteosarcoma

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR</th>
<th>95% CI (Wald)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin (mg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 240</td>
<td>1.0</td>
<td>Reference</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 360</td>
<td>17.4</td>
<td>3.1–96.8</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 15.5</td>
<td>1.0</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 – 15.5</td>
<td>2.8</td>
<td>0.8 – 9.8</td>
<td>0.099</td>
</tr>
<tr>
<td>≤ 12</td>
<td>6.4</td>
<td>1.6 – 25.4</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Mulrooney et al. BMJ. 2009, Dec 8; 339
Main long term side effects in survivors after a cancer in TYA

Hazard Ratio

59%  24%  7.5%  7.8%  6.8%

Brewster, BJC, 2014
Fertility preservation: a prerequisite before beginning cancer treatment in TYA

- INFORMATION about fertility issues in all cases
- SPERM BANKING in men
- FERTILITY PRESERVATION before or after treatment in females according to risk
Long term follow-up

- Systematic plan for screening, surveillance, and prevention
- Adapted to the risks associated to
  - previous cancer,
  - cancer therapy,
  - genetic predispositions identified or suspected,
  - lifestyle behaviors,
  - Comorbidities
- Life-long in high risk patients
• European Network for Teenagers and Young Adults with Cancer
• EMSOS- SIOPE group
• Several national groups for TYA oncology
Several models of care

TYA units allowing to have

- a multiprofessional team trained to TYA oncology
- Involvement of both pediatric and adult oncologists in the same structure
- Access to all clinical trials available for this age group
- Environment adapted to this group of patients
- Pairs groups

Organ centered care

- patients are treated by organ specialists
- with the help of a multi-disciplinary teams dedicated to provided age appropriate TYA support
Cancers in TYA

- More than 75% of TYA with cancer will survive.
- The quality of care (including choice of 1st line treatment, environment, psycho-social support, long term follow-up) of major importance to improve their quality of life after cancer treatment.

- For those patients with high risk cancer collaborations between all groups to foster research and access to new drugs is crucial.
Thanks