The specific needs of adolescents and young adults undergoing ASCT

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ASCT in AYA

• What’s an AYA?
• Epidemiologic data
• Therapeutic specificity and evolution.
  – Acute lymphoblastic leukemia
  – Chronic myeloid leukemia
  – Sickle cell disease
• Specific problems: adherence and fertility
• ASCT in AYA: how and where?
AYA : In-between generation

- Pediatric hospitals:
  >90% of patients less than 15y

- Adult hospitals:
  >90% of patients more than 40y

No specific organisation for adolescents and young adults
Adolescence

• Adolescence = intermediary stage between childhood and adulthood
• WHO definition = 10-19y

• Onset with puberty or earlier?
• End with the acquisition of certain rights:
  – driving a vehicle, marrying, purchasing alcohol, voting…

• Depend on culture, ethnicity, country…
"A body goes through changes during the teen years. When you started dating, my hair turned gray. When you started driving, I got heart palpitations..."
Adolescence development

• Physical development:
  – Rapid growth
  – Acquisition of secondary sex characteristics

• Cognition development:
  – Abstraction,
  – Acquisition good decision-making skills

• Emotional development:
  – Self-esteem
  – Sexual identity

• Social development:
  – Going away from parents
  – Joining peer groups (dress, behave alike…)

Cancer and Therapy

What are you actually doing here?
ASCT
Epidemiologic data
Allogeneic transplantation
Principal indications

- Hematological malignancies +++
  - Acute leukemia (ALL/AML)
  - Lymphomas
  - Myeloproliferative and myelodysplastic syndromes
- Bone marrow failure
  - Severe aplastic anemia
  - Inherited diseases (fanconi disease…)
- Hemoglobinopathies
  - Sickle cell disease
  - Thalassemia
Cancer in children / Epidemiology

Cases = 36,446
Rate = 165.92 per million

Li E, Pediatrics 2008
Cancer in AYA / Epidemiology

15- to 19-Year-Olds

- Lymphomas: 26%
- Leukemia: 12%

20- to 24-Year-Olds

- Lymphomas: 22%
- Invasive Skin*: 14%
  - *82% Melanoma
- Male Genital System: 13%
- Other: 2%
- CNS: 7%
- Female Genital System: 8%
- Endocrine System**: 9%
- **87% Thyroid
- Male Genital System: 8%
- Digestive System: 3%
- Bones & Joints: 3%
- Soft Tissue: 3%
- Oral Cavity & Pharynx: 3%
- Respiratory System: 2%
- Urinary System: 2%
- Other: 2%
Outcome improved?

Stelianova-Foucher E, Lancet 2004
Shared progresses?
Why?

• Varying reasons among countries
• Social issues
  – Unemployment
  – Insurance
• Psychological issues
  – Delay in care initiation
  – Minimization of symptoms
• Decreased inclusion in clinical trials
Therapeutic specificities and evolution in transplant indications
ASCT in AYA
Epidemiology

- Société Française de Greffe de Moelle et de Thérapie cellulaire

- Register data (PROMISE)
  - Transplant performed since 2001
  - N=12184 (ASCT)
Adult or pediatric department?

A (15-19y, N=772) YA (20-25y, N=628)

Mixt Dept
Ped Dpt
Adult Dpt
ASCT in AYA
Epidemiology

• Saint-Louis Hospital, Paris
  – Mixt center (adult and children transplantation unit)
  – Bone marrow failure reference center

• Retrospective study
  – N=2298 allogeneic transplantation (1st only)
  – N=282 Adolescents (15-19y, 12.4%)
  – N=178 YA (20-24y, 7.7%)
  – Enrollment period :1973-2011
    • <1990 N=580
    • 1990-1999 N=725
    • 2000+ N=793
ASCT Indications

Children N=639
A (15-19y) N=282
JA (20-24y) N=178
Ad1 (25-39y) N=601
Ad2 (40y+) N=598

- Hemoglobinopathies
- Plasma cell disorders
- Lymphoma
- MDS / MPD (Ph1neg)
- Chronic Leukemia
- Bone Marrow Failure
- Acute Leukemia

Others
Evolution of ASCT indications

Ados (15-19y)

JA (20-25y)

Comparison of ASCT indications in different age groups:

- **<1990**
- **1990-1999**
- **≥ 2000**

Key indications:
- Others
- Hemoglobinopathies
- Lymphoma
- MDS / MPD (Ph1neg)
- Chronic Leukemia
- Bone Marrow Failure
- Acute Leukemia

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;1990</th>
<th>1990-1999</th>
<th>≥ 2000</th>
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</thead>
<tbody>
<tr>
<td>Ados (15-19y)</td>
<td><img src="chart1.png" alt="Bar Chart" /></td>
<td><img src="chart2.png" alt="Bar Chart" /></td>
<td><img src="chart3.png" alt="Bar Chart" /></td>
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<tr>
<td>JA (20-25y)</td>
<td><img src="chart4.png" alt="Bar Chart" /></td>
<td><img src="chart5.png" alt="Bar Chart" /></td>
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</table>
AYA / Evolution of donor source

<1990  1990-1999  ≥ 2000

Ados (15-19y)

YA (20-24y)
AYA / ALL

Ados (15-19y)

YA (20-24y)
AYA with ALL

• Indications for ASCT in CR1
  – Adolescent mostly treated in pediatric trials
    10-15% of patients
  – Young adults treated in adult trials
    1/3 of patients

• Increased rate of relapse in adolescents treated in adult trials.
Comparison Adult vs Ped. Trials in adolescents (15-19y)

5y-EFS

FRALLE 93
67 % (± 13)

LALA 94
41 % (± 14)

P<0.0001
AYA / ALL

Ados (15-19y)

YA (20-24y)
Distribution of ASCT in Sickle cell disease according to age (Saint Louis hospital experience, Paris)
Evolution of ASCT performed for SCD in adolescent
(Saint Louis hospital experience, Paris)

- <1990: N=93
- 1990-1999: N=82
- ≥ 2000: N=107

- 6% Sickle cell disease
- Others
Indications of transplant in SCD

1. Allogeneic BMT is widely used in children with an HLA identical sibling donor.

2. In contrast few data exist in adults because ASCT is considered too toxic in these patients

3. However, a recent report shows the feasibility of MA ASCT in patients older than 16 y, with encouraging results in term of survival without disease
Results of ASCT according to the age in SCD
(french experience)

Age at transplant:  
- < 16 y
- > 16 y (16-27)

Event-Free Survival probability (%)

Number at risk
Group: 0
130 83 55 30 23 11 8 2 1 1 1 1
Group: 1
12 2 2 2 2 0 0 0 0 0 0 0

Years post-Transplant
Evolution of ASCT performed for chronic myeloid leukemia in the AYA
(Saint Louis hospital experience, Paris)

In adults:
The first line treatment: TKIs. (Gleevec)
ASCT is performed in treatment failure.

- Ados (15-19y)
- YA (20-24y)
The best front-line treatment in children and adolescents: TKIs or ASCT?

**TKIs:**
- Long term toxicity unknown

**ASCT:**
- Less transplant related mortality and morbidity than in adults
- Problem of infertility.

Clinical data lack to conclude

Current recommendations: TKIs in front line and ASCT in treatment failure
• Differences in ASCT indications between Ados and YAs are poorly supported by disease disparities.
• This differences mosly reflect the gap between pediatric and adult care programs.
• One major goal for AYA programs =

   Close collaboration
   between pediatric and adult hematology
Specific issues:

Fertility preservation
Post-transplant infertility issue

• Conditioning regimen administrated before transplant usually leads post-transplant infertility

• The risk of post-transplant infertility depends on the type and the dose of treatment (high dose of alkylating agent, TBI) and the patient age

• 73% of cancer survivors age 12-28 y at diagnosis reported they wanted a child in the future

• Post-transplant fertility preservation has a significant impact on the quality of life

• Take care of a fertility preservation means that there is life after treatment

Fertility preservation is a major goal in transplant of AYA
Options for female fertility preservation:

1. Fertility cryoconservation
2. Oocyte cryoconservation
3. Ovarian tissue freezing and grafting
Embryo cryopreservation: the different steps

Ovarian stimulation

↓

Oocyte retrieval

↓

Fertilization

↓

Transfer of the embryo into the uterus

(after a period of storage and freezing)
Embryo cryopreservation: advantages and disadvantages

- The most effective technique (thousands of births)
- Pregnancy rate: about 20% per embryo transfer
- Performed in all the in vitro fertilization centers

- Requirement of a male partner
- Need of time (10-14 j) for ovarian hormonal stimulation
- Prohibition of use of embryo if the couple separates
Mature oocyte cryopreservation: advantages and disadvantages

- No requirement of a parter
- Paucity of mature oocytes
- Not possible before the puberty
- Need of time for ovarian hormonal stimulation
- Freezing problem due to the fragility of the oocyte

Results:
- 936 births
- Low rate of congenital abnormalities (1.3%)
Ovarian tissue freezing and grafting: the different steps

1. Laparotomy
2. Removal of an ovary
3. Ovarian slicing
4. Freezing
5. Transplantation of ovarian fragments after ASCT
Ovarian tissue freezing and grafting: advantages and disadvantages

- Potential source of many immature oocytes
- No need of ovarian stimulation
- Feasibility before the puberty
- Facility to freeze

Results:
- Only 7 births

- Risk with the laparoscopic procedure
- Risk of malignant cell transfer: contrindication in leukemia and lymphoma
- Research: in vitro maturation of immature oocytes
Options for male fertility preservation:

- Sperm banking: the most reliable and well-established technique.
  - Limitations: inability of ejaculate related to age, discomfort level and illness
  - Invasive alternatives: microsurgical epididymal sperm aspiration, testicular sperm extraction, electroejaculation
  - Currently, intracytoplasmic sperm injection requires the removal of only a few viable sperm

- Cryoconservation and transplantation of spermatogonial and testicular tissue: experimental techniques
# Pregnancy after autologous and allogeneic SCT

<table>
<thead>
<tr>
<th>Total (N)</th>
<th>530</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>- Male (%)</td>
<td>52</td>
</tr>
<tr>
<td>- Female (%)</td>
<td>48</td>
</tr>
<tr>
<td><strong>Median age at transplant</strong></td>
<td>18-27y</td>
</tr>
<tr>
<td><strong>Interval ASCT- pregnancy</strong></td>
<td>5-10y</td>
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<tr>
<td><strong>Risk factor of infertility</strong></td>
<td></td>
</tr>
<tr>
<td>- Age</td>
<td>yes</td>
</tr>
<tr>
<td>- Myelo TBI</td>
<td>yes</td>
</tr>
<tr>
<td>- cGVHD</td>
<td>no</td>
</tr>
<tr>
<td><strong>Maternal and fetal complications</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Fetal death</strong></td>
<td>no more</td>
</tr>
<tr>
<td><strong>Congenital malformations</strong></td>
<td>no more</td>
</tr>
</tbody>
</table>
Specific issues:

Adherence of treatment plan
Definition

Elements associated with adherence:

- Patients’ self-care responsibilities
- Patients’ role in the treatment process
- Patients’ collaboration in health care provider
Prevalence of adherence in AYA

Adherence: usually poorer in AYA than in children an adults

• Studies in chronic disease such as asthma, diabetes, inflammatory bowel disease.

• In AYA treated for lymphoma or leukemia: non adherence range 27% to 60%

• Very few data after ASCT: specific issues of adherence include initial hospitalisation (4- 6 weeks), post-transplant follow up with frequent appointments, immunosuppressive drug taking
Causes and factors associated with lack of adherence in AYA (1)

- Opportunity to assert an independance from their family and the health care providers
- Poor involvement in all treatment decisions and management
- Poor understanding of the goals and expected benefits
- Poor support at participation in their usual activities,
Causes and factors associated with lack of adherence in AYA (2)

- Fear of the length of treatment and side effects
- Psychosocial context:
  - History of psychosocial difficulties
  - Psychological distress of parents, family conflict
  - Poor family relationship
  - Overly controlling relationship with parents or health workers
  - Lack of appropriate psychosocial supports, during treatment
How promote adherence in AYA? (1)

Communication +++

- Dialogue between health care providers, patient and family
- Clear and comprehensible information
- Use new sources of information (media, internet…)
- Allow a level of flexibility in treatment plan to accommodate motivating events and minimize interference with lifestyle
How improve adherence in AYA? (2)

• Early identification of risk factors:
  - Pre-existing family problems
  - Poor understanding
  - Socio-economic problem

• Assistance to the entourage
  - Psychological supports, financial aids
  - Parents’ home
AYA transplantation program

How and where?
How do they feel?  What do they want?

• N=347 (Survey in North London)
  – 53 % of young people who had been admitted to a paediatric ward, and
  – 81 % of those admitted to an adult ward, had felt out of place there;
  – 77 % thought a specific teenagers' room would be an improvement in service

Kari, Nurs Stand, 1999
AYA program

• Respect the confidentiality and privacy
  – Physical privacy (clothing, bathrooms, laminar air flow …)
  – Confidentiality when personal information is disclosed
  – Parental involvement discussed with patient

• Preserving family connections
  – Flexible visiting hours
  – Reevaluate neutropenic precautions during treatment

• Preserving socialization
  – Dedicated, multifunctional spaces
  – Activities (associations, recreational therapist …)
  – Communications with peers, school, colleagues …

• Education
  – School activities
  – Continuous education in young adults
AJA program

Space

• Dedicated inpatient space is rare, particularly in hematology / ASCT

• Hemato-oncology units mostly created in pediatric or adult departments -> limitations in age range recruitment.

• Creation of AYA units specifically dedicated to ASCT is disputable.
AJA program
Care

• Fertility preservation
• Psychosocial needs
  – Patient but also family, siblings (donor)
  – Proposed, not imposed
  – At all treatment stages (transplantation, follow-up, relapse, end of life, bereavement…)
• Pain management
• Palliative care
• Long-term follow-up
AJA program
Staff

• Trained and dedicated
• Bridge Adult and pediatrician expertise
• Composition :
  – AYA hematologist (Adult / Ped)
  – Nurse
  – Nutritionist
  – Psychologist
  – Social worker (education, employment, insurance)
  – Teacher
AJA program
Partners

• Specialists in:
  – fertility preservation
  – radiotherapist
  – infectious disease
  – endocrinology
  – dermatology…

• Recreational therapists
• Cosmetics experts

...
AJA program
Research

• Standardized care or clinical trials
• Evaluation:
  – Treatment efficacy/feasibility
  – Quality of life (cGVHD…)
  – Adherence to treatment (a/cGVHD, infections…)
  – Short and long-term adverse events
ASCT in AYA
Some current questions

• How previously non adherence to treatment may influence eligibility for ASCT?
• Does low adherence in AYA impact post-ASCT outcome?
• How to make neutropenic isolation more flexible to improve QOL during hospitalizations as inpatient?
• What is the long term impact on working/social life in adolescents?
Conclusion and perspectives:

• Currently few data about transplant in AYA:
  – Need for a better evaluation of specific outcomes of AYA after transplant, in term of survival, transplant-related mortality, GVH and relapse
  – Need of better evaluation of long term sequelae, QOL

• Management of ASCT in AYA:
  – Necessity of a multidisciplinary management: pediatric and adult physician, nurse, psychologist, social worker...
  – Management of late complications such as GVHD and sterility
  – Taking into account the impact of transplant on the working and social lifes
  – Interest for specific unit of treatment in AYA
Specificities of malignancy: biology, delay in diagnosis, pronostic factors

Psychological and physical changes

Compliance with treatment plan

Tobacco, alcohol, drug use

Future: professional and social life

Sexuality and fertility

Drug pharmacology: change in BMI, hormonal environment
Internet

• Source of controversial informations
  -> web site
• Emerging online peer groups:
  – Overcome physical limitations (immunosuppression, fatigue…)
  – Less expensive way to support patients
  – Minimize sociodemographic differences (sex, age, race…)
• Impact on care giver / patient relationships
  (Facebook, Twitter, chat…)