Fertility and gonadal failure

Alicia Rovó MD

Late Effects - Educational Day
Saturday 5/11/2011
Barcelona
Type of post-transplantation late effects

- Non-malignant late effects
- Malignant late effect
- Health status and social integration
- Quality of Life and sexuality
- Chronic Graft versus Host disease and immune reconstitution
Time of appearance of the different late effects after HSCT

Early complications:
- Respiratory complications
- Chronic GVHD and infections
- Keratoconjunctivitis
- Oral complications

Late complications:
- Thyroid dysfunction
- Growth failure
- Gonadal failure
- Chronic kidney disease
- Avascular necrosis
- Osteoporosis
- Dental caries
- Infertility
- Sexual dysfunction
- Abnormal cardiovascular risk factors

Very late complications:
- Cardiac complications
- Cardiovascular complications
- Liver Cirrhosis
- Malignant complications

Physical and psychological performance, QoL, social integration

Tichelli A et al. Exp Rev Hemat 2009, 2;5:583-601
Gonadal failure after HSCT

Depends

- Irradiation: dose and fractionation schedule of TBI
- Cytostatic drugs: type and dosage of the drug
- Age of the patient at the time of treatment
  - The younger the age, the better the chances for gonadal recovery

Conditioning regimen

- TBI 12-14 Gy
- Cyclophosphamide 120 mg/kg
- Etoposide VP16 60 mg/kg
- Combination of Busulfan (16 mg/kg) and Cyclophosphamide (120 mg/kg)
How to assess gonadal failure?

**Should be according to**
- Sex and age of the patients
- Specific questions:
  - puberty
  - therapy issues: i.e hormonal replace therapy
  - motherhood/ fatherhood wishes
  - assisted conception
  - contraception
  - sexual life

**Evaluation**
- Hormonal levels test
  - FSH/LH
  - Estradiol /Testosterone
  - Anti-Müllerian hormone
  - Inhibin-B

- Sperm fluid analysis

- Multidisciplinary approach
Fertility markers
Anti-Müllerian hormone

**In women:**
- expressed by granulosa cells of the ovary during the reproductive years
- controls the formation of primary follicles (by inhibiting excessive follicular recruitment by FSH)
- Results should be compared to average levels
  - Useful in fertility assessment in combination with other tests (FSH/LH/estrogen/transvaginal ultrasound)
  - Provide a guide to ovarian reserve (pre-pubertal)

**In males**
- is produced in Sertoli cells of the testes
- ↑ throughout childhood in males but declines to low levels during puberty and adult life
Fertility markers

**Inhibin-B**

down regulates FSH synthesis and inhibits FSH secretion

**In females:**

*Inhibin B* reaches a peak in the **early- to mid-follicular phase**

**In males:**

- produced in Sertoli cells.
- contribute to regulate spermatogenesis
- can be use as a marker for fertility
  - is **higher among fertile men**
Ovarian failure

- 99% females developed evidence of gonadal dysfunction after HSCT
- **Hypergonadotropic hypogonadism is almost the rule:**
  - ↑ serum follicle-stimulating hormone (FSH)
  - ↑ luteinizing hormone (LH)
  - ↓ estradiol
  - risk factors:
    - older age
    - conditioning regimens TBI and Busulfan based
  - arises **very early** after HSCT (earlier in comparison to males)
  - Symptoms:
    - amenorrhea
    - menopause

Jadoul et al. BMT 2011
Puberty should not be delayed after the age of 13
Spontaneous menarche can be observed
Puberty should not be delayed after the age of 13
Early puberty is a rare event
  - (need to be treated with gonadotropin releasing hormone-agonist)
Inhibin B may help in counselling at pubertal age
  - (concordance between ↑ FSH and inhibin B)
Low Anti-Müllerian hormone suggest that there is a major loss of primordial follicles

Laporte S et al. BMC Pediatr 2011;25:11-20
A Borgmann-Staudt et al. BMT (2011), 1–6
## Ovarian failure

### Menopausal symptoms
- more frequently reported
  - vasomotor (90%)
  - musculoskeletal symptoms (61%)
  - vulvo-vaginal atrophy (54%)
  - mood changes (54%)

### Hormonal replacement therapy after HSCT

**Indications:**
- premenopausal women age (<45 years)
- absence of:
  - liver toxicity
  - complete remission
  - underlying malignancies post-SCT (BC)
  - coronary artery disease
  - venous thrombosis
  - subjective refusal

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*Piccioni P et al. Maturitas 2004;49,4:327-333*


*Nakayama K et al. BBMT, 2009 Nov;15(11):1465-74*
Ovarian failure

- Up to 90% of adult female patients require HRT after HSCT
- This replacement therapy can be interrupted every 1-2 years to evaluate spontaneous recovery
- Ovarian failure in young long-term survivors can affect health status, sexual life and QoL

*Piccioni P et al. Maturitas 2004;49,4:327-333*


*Nakayama K et al. BBMT, 2009 Nov;15(11):1465-74*
Gonadal failure in males

- Endocrine dysfunction of the testis is less pronounced
- Testosterone levels are usually normal
  - Leydig cells are more resistant to chemotherapy and irradiation than the Sertoli cells
- Usually the serum FSH levels are increased, but LH normal
- Sex-hormone replacement will not be necessary
  - despite reduced or absent spermatogenesis

Pre-pubertal boys:
- in most cases will enter puberty spontaneously
- at the age of 9 years the determination of LH/FSH is recommended
- Induction of puberty should not be delayed after the age of 14 years

Sanders et al. Blood 2009;113:306-308
Fertility after HSCT in childhood and adolescence

N=344 from 7 pediatric EU centers
Male 60%
Median age at study: 19 (12-35) y
Median follow-up: 6 (3-12) y
Overall infertility rate: 75%
  83% in female
  69% in males

Fertility rate:
- Malignancy: 21%
- Non-malignant: 42%

Risk factors for infertility:
Females
- Start of treatment at age >13 years
- Conditioning with Busulfan
Males
- Conditioning with TBI
- Pre-pubertal therapy

<table>
<thead>
<tr>
<th>Pregnancies</th>
<th>Diagnosis</th>
<th>Date of birth</th>
<th>Date of HSCT</th>
<th>Conditioning regimen</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female patients (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ES</td>
<td>1982</td>
<td>2002</td>
<td>BU 12.8 mg/kg MEL 140 mg/m²</td>
<td>Healthy baby, born at term 2006</td>
</tr>
<tr>
<td></td>
<td>MDS</td>
<td>1983</td>
<td>2001</td>
<td>THIO 15 mg/kg FLU 160 mg/m²</td>
<td>Healthy boy, born at term 2007, amenorrhea after birth</td>
</tr>
<tr>
<td></td>
<td>SAA</td>
<td>1985</td>
<td>2003</td>
<td>CY 200 mg/kg</td>
<td>Healthy baby, born at term 2004</td>
</tr>
</tbody>
</table>

Male patients (n=2)

|             | SAA       | 1987          | 2003         | CY 200 mg/kg | 3 Healthy babies, all born at term, 2005, 2006, 2007 |
|             | SAA       | 1988          | 2004         | CY 200 mg/kg | Healthy girl, born at term 2010 |

A Borgmann-Staudt et al. BMT (2011), 1–6
Pregnancy outcomes after HSCT

- Retrospective study of the EBMT
  - 199 / 229 centers responded
- Information relating to 28'500 4-month survivors
  - Median follow-up time 6.5 years
- 312 conceptions registered in 232 patients / partners
  - In 113 patients and partners of 119 patients
  - 271 live births
- 30/232 (13%) – Artificial reproductive techniques
  - In vitro fertilization (n=10)
  - Hormonal stimulation (n=4)
  - Use of pre-transplant cryopreserved sperm (n=16)

*N. Salooja et al. Lancet. 2001; 358:271-276*
### Pregnancies and complications compared to normal populations

<table>
<thead>
<tr>
<th></th>
<th><strong>BMT</strong></th>
<th><strong>general population</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly birth rate</td>
<td>1.7 / 1000</td>
<td>12.5 / 1000</td>
</tr>
<tr>
<td>Multiple pregnancies</td>
<td>8 / 143 (6%)</td>
<td>1.4%</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>36 / 113 (32%)</td>
<td>6.2%</td>
</tr>
<tr>
<td>&lt; 37 weeks’ gestation</td>
<td>15 / 113 (13.3%)</td>
<td>5.9%</td>
</tr>
<tr>
<td>&lt; 2.5 kg birth weight</td>
<td>15 / 113 (13.3%)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Miscarriage/ ectopic pregnancy</td>
<td>14 / 143 (9.8%)</td>
<td>12.2%</td>
</tr>
<tr>
<td>congenital anomalies</td>
<td>3 / 113 (2.6%)</td>
<td>0.9-4%</td>
</tr>
</tbody>
</table>

*Source: N. Salooja et al. Lancet. 2001; 358:271-276*
Fertility after HSCT in SAA patients

Pregnancy/Fatherhood

- Non-SAA patients:
  - Prevalence of pregnancy/fatherhood after TBI conditioning less than 1%
- At 20 years posttransplant, the probability of an SAA patient to become pregnant/father
  - Pregnant: 47% (GVHD 26%; no GVHD 61%)
  - Father: 50% (GVHD 29%; no GVHD 62%)
  - Pregnancy of a SAA female usually uncomplicated

Fertility recovery and pregnancy in females
Fanconi anemia patients after HSCT

- 15 centers
- Patients transplanted between 1976-2008
- N= 101 female >16 years at HSCT
- **10/101 became pregnant (4/10 twice)**
  - Median age at HSCT 12 years
  - Conditioning: Cy with or without TBI
  - 5/10 patients showed ovarian failure
    - 2 recovery menses
    - 3 were under HRT
  - Pregnancies were 4-17 years after HSCT
  - Newborns all normal

*Nabhan et al. Haemat 2010;95(10):1783-1787*
Spermatogenesis after HSCT

N=64 males
Spermatogenesis until up to 10y:
Cy N=10,90%
CyBu or thiotepa
N=6, 50%
Cy+TBI, N=48, 17%

Figure 2 Recovery of spermatogenesis after BMT (percentage of patients) according to the conditioning regimen.

Spermatogenesis after HSCT

Patients
- 62 invited to participate
- 5 had vasectomy before HSCT
- 18 declined

### Spermatogenesis after HSCT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description according to WHO protocol*</th>
<th>N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoospermic</td>
<td>no spermatozoa</td>
<td>28</td>
</tr>
<tr>
<td>With spermatozoa</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>- Normozoospermic</td>
<td>&gt;20 million /mL</td>
<td>3</td>
</tr>
<tr>
<td>- Oligozoospermic</td>
<td>between 5 to 20 million/mL</td>
<td>1</td>
</tr>
<tr>
<td>- Severe Oligozoospermic</td>
<td>&lt; 5 million /mL</td>
<td>6</td>
</tr>
<tr>
<td>- Cryptospermic</td>
<td>spermatozoa were detected only after centrifugation</td>
<td>1</td>
</tr>
<tr>
<td>Normal Motility</td>
<td>when at least &gt;50% of spermatozoa were motile</td>
<td>7</td>
</tr>
<tr>
<td>Normal Morphology</td>
<td>when more than &gt;25% of total spermatozoa had a normal morphology</td>
<td>None</td>
</tr>
</tbody>
</table>

SFA results

N=224

N=31
No Busulfan and no TBI

N=44
Busulfan regimen

N=146
TBI regimen

P<0.0001

<table>
<thead>
<tr>
<th>Condition</th>
<th>N=31</th>
<th>N=44</th>
<th>N=146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normozoospermia</td>
<td>10 (32%)</td>
<td>10 (23%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Oligozoospermia</td>
<td>3 (10%)</td>
<td>5 (11%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Severely oligozoospermia</td>
<td>5 (16%)</td>
<td>9 (20%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Cryptospermia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>13 (42%)</td>
<td>20 (46%)</td>
<td>119 (81%)</td>
</tr>
</tbody>
</table>
Analysis of patients with SFA before and after HSCT

• 28 patients evaluable before HSCT
  – Spermatozoid could be detected in 27 (96%): 
  – 20 (71%) of them presented normozoospermia, 
  – 4 (14%) oligozoospermia 
  – 3 (11%) severe oligozoospermia  
  – 1 (4%) azoospermia. 
  – All patients with decreased sperm counts in the pretransplant SFA had 
    • malignant disease (AML 3; CML 2; Lymphoma 2; MDS/MPN 1) 
    • most of them were heavily pretreated. 

• 17/28 patients evaluable after HSCT
  – 14/17 (82%) had azoospermia, 
  – one oligozoospermia 
  – two severe oligozoospermia. 

Rovó A. et al. ASH meeting 2010
Manuscript submitted October 2011
SFA follow-up after HSCT

- 58 patients
- Median time 1st and last SFA:
  - 24 months (1.5 – 140)
- Sperm concentration
  - In 12/58, 21% there was an increase in sperm counts
  - 36 patients were azoospermic in first and last SFA
- Recovery of spermatogenesis was time depending
  - Longer FU between 1st-to last SFA

Rovó A. et al. ASH meeting 2010
Manuscript submitted October 2011
## Risk factors for azoospermia

### Univariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>Azoospermic</th>
<th>Evidence of spermatogenesis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI (≥7.5 Gy)</td>
<td>146</td>
<td>119 (82%)</td>
<td>27 (18%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>142</td>
<td>104 (73%)</td>
<td>38 (27%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>134</td>
<td>99 (74%)</td>
<td>35 (26%)</td>
<td>0.063</td>
</tr>
<tr>
<td>Extensive chronic GVHD</td>
<td>51</td>
<td>41 (80%)</td>
<td>10 (20%)</td>
<td>0.062</td>
</tr>
<tr>
<td>cGVHD at time of last SFA</td>
<td>63</td>
<td>52 (83%)</td>
<td>11 (17%)</td>
<td>0.004</td>
</tr>
<tr>
<td>On IS at time of SFA</td>
<td>52</td>
<td>41 (79%)</td>
<td>11 (21%)</td>
<td>0.058</td>
</tr>
<tr>
<td>&gt; 25 years of age at HSCT</td>
<td>87</td>
<td>69 (79%)</td>
<td>18 (21%)</td>
<td>0.010</td>
</tr>
<tr>
<td>&lt; 8 years time interval</td>
<td>148</td>
<td>109 (74%)</td>
<td>39 (26%)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Rovó A. et al. ASH meeting 2010

Manuscript submitted October 2011
Ongoing cGVHD is a main risk factor for azoospermia in patients not conditioned with TBI

**Multivariate analysis**

<table>
<thead>
<tr>
<th>All patients</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>– TBI present</td>
<td>7.130</td>
<td>3.415-14.887</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>– Age &gt;25 years at HSCT</td>
<td>2.406</td>
<td>1.094-5.292</td>
<td>0.029</td>
</tr>
<tr>
<td>– Chronic GVHD at time of SFA present</td>
<td>2.178</td>
<td>0.950-4.993</td>
<td>0.066</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All patients excluding TBI as a variable</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Chronic GVHD at time of SFA present</td>
<td>2.576</td>
<td>1.221-5.434</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Can we predict the risk to remain azoospermic?

2 points
- TBI

1 point
- Age > 25 y at HSCT
- Ongoing cGVHD

0.5 point
- Time between HSCT and SFA < 8 years.

<table>
<thead>
<tr>
<th>Score</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0 – 1</td>
<td>1.5 – 3</td>
<td>3.5 – 4.5</td>
</tr>
<tr>
<td>Azoospermia / Total</td>
<td>10 / 28</td>
<td>67 / 100</td>
<td>55 / 60</td>
</tr>
<tr>
<td>Azoospermia (%)</td>
<td>36%</td>
<td>67%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Rovó A. et al. ASH meeting 2010 Manuscript submitted October 2011
### Age at transplantation and paternity before HSCT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Paternity before HSCT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients at risk</td>
<td>yes: 211, no: 50 (24%), 161 (76%)</td>
<td>-</td>
</tr>
<tr>
<td>Median age at HSCT</td>
<td>24 (2-59), 36 (22-59), 21 (2-55)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- 90% of the patients who had children before HSCT were older than 25 years at HSCT time
- 28% of the patient without children before HSCT were older than 25 years at HSCT time

Rovó A. et al. *ASH meeting 2011*
### Paternity before HSCT

<table>
<thead>
<tr>
<th>Paternity before HSCT</th>
<th>50 / 211 (24%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of children before HSCT</td>
<td>84</td>
</tr>
</tbody>
</table>

#### Bar Chart

- **No child**: 161
- **One child**: 25
- **Two children**: 19
- **Three children**: 3
- **Four children**: 3

*Source: Rovó A. et al. ASH meeting 2011*
Paternity after HSCT

<table>
<thead>
<tr>
<th>Paternity after HSCT</th>
<th>29/ 211(14%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of children after HSCT</td>
<td>44</td>
</tr>
<tr>
<td>Time interval between HSCT and the first child (years)</td>
<td>7.2 (1-21.6)</td>
</tr>
</tbody>
</table>

Rovó A. et al. ASH meeting 2011
Does paternity before HSCT influence behavior of long-term recipients?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients at risk</th>
<th>Paternity before HSCT</th>
<th>No paternity before HSCT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>211*</td>
<td>50 (24%)</td>
<td>161 (76%)</td>
<td>-</td>
</tr>
<tr>
<td>N paternity after HSCT</td>
<td>211</td>
<td>5/50 (10%)</td>
<td>24/161 (14%)</td>
<td>0.804</td>
</tr>
<tr>
<td>Wishes of paternity</td>
<td>145</td>
<td>3/30 (20%)</td>
<td>90/115 (78%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cryopreservation of sperms before HSCT</td>
<td>150</td>
<td>5/31 (16%)</td>
<td>30/119 (25%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Adopted child</td>
<td>132</td>
<td>0/30</td>
<td>4/102 (4%)</td>
<td>0.344</td>
</tr>
</tbody>
</table>

*12% of the patients were younger than 15 years at HSCT
** 11 unknown cases in respect of adoption
Does RIC reduce gonadal dysfunction after HSCT?

What do we know

- RIC reduces acute toxicity
- In general long-term effects of RIC are unknown
  - Exception: gonadal failure
    - Experience in SAA patients conditioned without TBI clearly showed:
      - reduced toxicity
      - good chances for recovery
- Ongoing EBMT studies
- Probability of chronic GvHD not reduced

Type of post-transplantation late effects

Gonadal failure

- Non-malignant late effects
- Malignant late effect
- Health status and social integration
- Quality of Life and sexuality
- Chronic Graft versus Host disease and immune reconstitution
Type of post-transplantation late effects

**Gonadal failure**

- Non-malignant late effects
- Malignant late effect
- Health status and social integration
- Quality of Life and sexuality
- Chronic Graft versus Host disease and immune reconstitution
Gonadal failure

Summary

It is a very frequent long-term sequela

It requires:

- Monitoring gonadal function
- Monitoring fertility
- Patient counseling
  - before HSCT
  - along follow-up post HSCT
- Counseling issues
  - symptoms/treatment related to gonadal failure
  - fertility prevention/recovery
  - contraception
  - sexual life
Thank you very much for your attention