The effects of cancer treatment on male infertility

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Disclosure statement

“I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content”
This lecture includes

- Spermatogenetic recovery after low and high dose exposures
- What factors contribute to impaired spermatogenesis?
- Effect of follow-up time for spermatogenetic recovery

International Harmonisation Group / PCSF-WP6, Male Gonadotoxicity Guidelines Group

Skinner et al. Lancet Oncol 2017; 18: e75–90

Cancer therapy

Impact of chemotherapy and irradiation on testicular function depends on
- Type of drug used
- Dosage
- Fractionation schedule for radiation
- Age at treatment, only Leydig cell function
  - no evidence that age at exposure is associated with susceptibility to spermatotoxicity
- Time since treatment (slow recovery)
- Genetic variation
Effects of high dose cancer therapy in testis

- Spermatogenesis is stem cell driven system
- Toxic insult with HIGH INTENSITY
  - Depletes spermatogonial stem cell pool
    → Permanent spermatogenetic failure = azoospermia
- Toxic insult with NEARLY STERILIZING INTENSITY
  - Surviving spermatogonial stem cells begin to proliferate and repopulate the tubules
    → Recovery follows, but takes time!

Recovery at different stages of spermatogenesis

- Even moderate gonadotoxic doses produce azoospermia that lasts longer than the 12 weeks
- Recovery is delayed for months or decades if gonadotoxic therapy kills stem cells
Recovery of spermatogenesis depends on the dose of irradiation

≥0.1 Gy
The differentiating spermatogonia are killed → short term cessation of spermatogenesis

2–3 Gy
Kills also SSCs → long term azoospermia.

>6 Gy
Able to deplete the SSCs pool →permanent/long term infertility

Spermatogenetic recovery after hematopoietic stem cell transplantation in adults

Recovery of spermatogenesis after allogeneic HSCT is predicted by
• younger age (<25 years)
• a non–total body irradiation (TBI)-based conditioning regimen
• no treatment for the underlying malignancy before HSCT
• no chronic graft-versus-host disease


Mitchell et al. Male Hypogonadism: Basic, Clinical and therapeutic Principles
Male fertility after allo HSCT

- Pregnancy rates for partners of male patients after allogeneic transplantation in EBMT database is <2%
- for SAA patients 5.3%, acute leukemia 0.8%
- No fertility data on reduced-intensity conditioning protocols
- No fertility data for pediatric HSCT recipients
- An increased incidence of prematurity and low birth weight (LBW) among the single spontaneous pregnancies fathered by HSCT survivors

Effects of low dose cancer therapy in child and adult testis

Child
- No morphological effects

Adult
- Differentiating spermatogonia are killed
- Spermatocytes and spermatids survive and continue their maturation into sperm but are not replaced by new cells
  → some sperm production 4-10w (do not cryopreserve!)  
  → short term loss of sperm production and recovery
Conventional leukemia therapy and acute depletion of the spermatogonia

Median age at testicular biopsy 5 (1-16) years, n=37

No difference in total sperm count after a follow-up period of 9-19 years between non-alkylating vs alkylating therapy

Poganitsch-Korhonen et al. Leukemia 2017;31:1460-1463.

Cumulative rate of first fathered child by age of men

Childhood acute leukemia

Follow up 20y (range 11-30), n=50

Leukemia therapy with 0-10 g/m² cyclophosphamide does not affect early male fertility

No fertility after Cyclophosphamide>20g/m²

Sperm quality after spermatogenetic recovery

- The recovery is almost always progressive, and significant declines in sperm counts are rarely observed (Cave! CNS irradiation)
- Many recover to normospermic levels
- When the human testis contains <3–4 million sperm, sperm do not survive epididymal transit and do not reach the ejaculate
- It is possible that some sperm are produced in the testis. Recovery may be patchy.
- Spermatozoa can be retrieved from the testes by microdissection testicular sperm extraction (TESE)

What factors contribute to impaired spermatogenesis?

Risk of long term/permanent infertility is associated with treatment with

Alkylationing agents
- Cyclophosphamide
- Nitrogen mustard
- Procarbazine


→ Sperm concentration decreases with increasing cumulative dose
→ No threshold dose for azoospermia can be identified – genetic variation!
What factors contribute to impaired spermatogenesis?

Risk for permanent infertility is associated with radiotherapy

- Exposing testes at any dose
- Especially doses >2-3 Gy
- Especially TBI (level C)


There is no evidence of

- Safe irradiation dose

Gaps in knowledge Impaired Spermatogenesis

- Risks of, and dose thresholds, for impaired spermatogenesis of
  - Radiotherapy exposing the testes, including those treated with TBI
  - Busulfan, chlorambucil, ifosfamide, melphalan and thiopeta
  - Dacarbazine, procarbazine, temozolomide
  - Carboplatin, cisplatin
  - Carmustine, lomustine

- Role of genetic susceptibility in development of impaired spermatogenesis

- Impact of follow up time
Fertility data matures slowly

Childhood cancer survival

Modern era
Precision medicine

Year of Diagnosis

Proportion surviving after 2 years [%]

Puberty
Early fertility
Final fertility

Adult testicular volume reflects recovery of spermatogenesis after pediatric HSCT

Follow up 13 ± 4.8 y, median age at study 22 ± 6.0 years, n=106

Mean adult testicular size is >15 ml after
• busulfan-based regimes
• cyclophosphamide alone as conditioning

→ suggest very long-term recovery of spermatogenesis after chemotherapy-based regimens

Wilhelmsson et al PBC 2014;61:1094-100.
Spermatogenetic recovery after pediatric HSCT is progressive

Preliminary HSCT data Helsinki-cohort, n=41 with no testosterone replacement

Follow up 16.1 ± 5.7 y, median age at study 26.1 ± 6.3 years

Spermatogenetic recovery depends on cumulative testicular irradiation dose

Preliminary HSCT data Helsinki-cohort, n=41 with no testosterone replacement
Predictors of total sperm count in multivariate analysis

Preliminary HSCT data Helsinki-cohort, n=41 with no testosterone replacement

Follow up 16.1 ± 5.7 y, median age at study 26.1 ± 6.3 years

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<tr>
<th>Predictor</th>
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<tr>
<td>Cum testicular irradiation dose</td>
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<td>Time from HSCT</td>
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<td>Testicular volume</td>
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Future challenges for fertility preservation of young boys

- How to counsel patients and parents?
- How to offer tissue preservation to right patients?
- What is the right timing for fertility preservation?

Multi-disciplinary teams are required
Thank you