Effect of chemo- or radiotherapeutic agents on human sperm: the reproductive needs of young male cancer survivors

Ghamartaj-Hosseini

Tutor: Hervé-Lucas

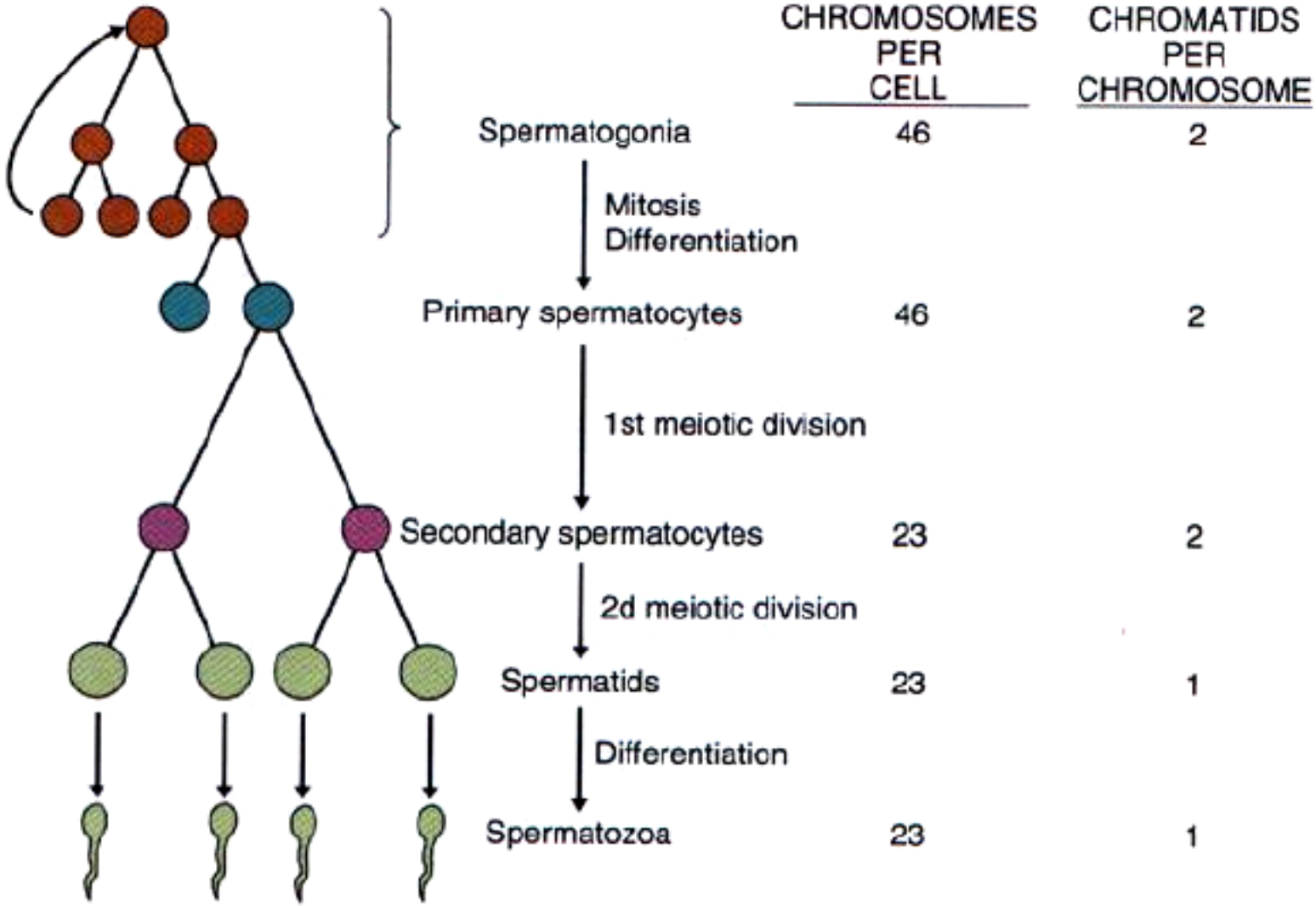
Over the past 25 years, there has been an increase in the diagnosis of malignancy in men of reproductive age around the world.

Since survival of these young patients is approaching 80% and most of them receive chemotherapy or gonadal irradiation, reproductive dysfunction is a significant concern.

The aim of the study

To provide an overview of the gonadotoxic effect of chemo- or radiotherapy, and to assess the cytoprotective measures that may improve the recovery of spermatogenesis after cancer treatment.

Spermatogenesis



developing spermatogonia > stem cells > spermatocytes > speramtides > spermatozoa

Gonadotoxic effect of Irradiation

- Dose-dependent effect on the testis

- Inflicts damage on the cellular DNA, resulting in single and double strand DNA breaks of developing spermatogonia and spermatocytes leading to subfertility or azoospermia

Recovery of spermatogenesis after irradiation

Dose (Gy)	Recovery time
> 0.1	9-18 months
0.15-0.4	10-18 months
0.4-2	2-5 years
2-6	> 5 years

(Yeung et al., 1998)

Gonadotoxic effects of chemotherapeutic agents are related to:

- class of agent used: alkylating agents- nitrogen mustard
  antimetabolite- antitumor antibiotics, e.t.c
- route of administration
- dose
- frequency of treatment
- combined chemotherapy
- recovery time depends on the degree of damage inflicted to the primary spermatogonia

Genetic lesions in human sperm following chemo- or radio-therapy

- Increased chromosomal fragmentation after radio- and chemo-therapy (Es-Slami et al., 1996; Chatterjee et al., 2000)

- Multiple structural abnormalities immediately after radiotherapy in postmeiotic spermatids and spermatozoa (Rousseaux et al., 1993)

- Increased aneuploid frequency (chromosome 1, 6, 11, X and Y) in spermatozoa after chemotherapy and radiotherapy (Monteil et al., 1997; Robbins et al., 1997)

Summary (I)

The ultimate ability of sperm production recovery and function after therapy is multifactorial. The final recovery time depends on the degree of injury to the stem cells.

Prospective studies are essential to develop treatment regimens that will cause less damage to the male reproductive function.

Summary (II)

It would have been of interest to follow the sperm chromosomal aberration rates in young men cancer survivors. The results will be used to compare the mutagenic potentials of different cancer treatment regimens and determine whether the mutagenic effects are persistent or decline with time.

For prospective studies, sperm collections should be planned before cancer treatment and at regular intervals during and after treatment.

This information would be extremely valuable in the reproductive counselling of long-term survivors of cancer therapy.

Cytoprotective measures

- Hormonal treatment
- Antioxidant treatment

Hormonal recovery of spermatogenesis after cancer treatment

• Hormonal treatment was supposed to protect testis by interrupting the pituitary-gonadal axis, reducing the rate of spermatogenesis, and rendering the resting testis more resistant to chemo- or radio-therapy.

• Since the target cells for prolonged reduction in spermatogenesis are spermatogonia, this treatment has been assumed to render spermato-gonia quiescent.

Clinical study

- Testosterone given to men before and during an 8-month cycle of cyclophosphamide therapy resulted in a shorter recovery time for spermatogenesis (Masala et al., 1997)

- GnRH agonists have also been used in men during chemotherapy which showed inconclusive results. (Kreuser et al., 1993; Johnson et al., 1985)

Antioxidant treatment for recovery of spermatogenesis

↑ Damage to DNA

↓ ↑

↑ Reactive oxygen species (O_2^-, H_2O_2,OH^-, $ONOO^-$)

↓

↓ Antioxidant (SOD, Catalase, vitamin E, C, b-carotene, GSH)

↑ Oxidative stress

↓

↑ LPO in sperm

↓

↓ Motility, viability, capacitation, Acrosome reaction
Sperm Function

↓

↓ Fertility

Perspective

The development of new hormonal treatments, as well as reactive oxygen scavengers, may decrease testicular injury from chemotherapeutic and radiation treatment regimens.