Testicular biopsies in young boys diagnosed with cancer to preserve future fertility- towards a safe and feasible autologous cell therapy in future.

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1. To preserve testicular tissue of young boys with cancer with high risk of infertility for possible autologous transplantation in the future if infertility has become apparent, and to identify germcells in the testicular tissue.2. To gain insight...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON52444

Source
ToetsingOnline

Brief title
PRINCE project

Condition

- Other condition

Synonym
preserving fertility

Health condition

jongens met kanker en hoge kans op onvruchtbaarheid

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor kinderoncologie
Source(s) of monetary or material Support: Ministerie van OC&W,stichting Bergh in 't Zadel

Intervention

Keyword: Boys, Fertility, Preservation, Therapy

Outcome measures

Primary outcome

-Successful cryopreservation of testicular tissue in which germ cells can be identified for later use in auto transplantation and follow up of previous cohort (Amsterdam UMC, location AMC) to register possible late complications. The presence of SSCs will be identified based on histological analyses (immuno-) characterization, possibly supported by flowcytometry and single cell sequencing

-Successful sampling and storage of testicular tissue (cryosurvival of SSCs, ability to propagate SSCs in vitro) in combination with long-term follow-up of possible side-effects of the testicular biopsy in the boy (local defects, endocrine and exocrine function of the remaining testis).

Secondary outcome

Long-term follow-up of possible side-effects of the testicular biopsy in the boy (local defects, endocrine and exocrine function of the remaining testis), post-pubertal fertility (as determined by semen analysis)and hormonal analysis (FSH LH testosterone and Inhibin B)

Study description

Background summary

More than 600 children per year are diagnosed with cancer in the Netherlands (www.kwf.nl). Due to effective cancer treatments for these children, more than 80% of them will now survive. Currently, one in 250 of the adults is expected to be a long-term survivor of childhood cancer (Brougham & Wallace, 2005). Given this apparent success in paediatric oncology, long-term adverse effects of cancer treatment are becoming increasingly important.
One of the major concerns with current treatment regimens are adverse effects on fertility. Our follow up data indicate that infertility is common in childhood survivors in general (~25%) and almost certain in young boys treated with high dose chemotherapy, high dose alkylating agents or radiotherapy to the testis region (Green 2014 lancet oncology p1215, Kenny 2018 JCO p2160). Having survived their cancer, many of these boys/men and their -future- partners wish to start a family just like other couples of reproductive age (van den Berg et al, 2007).
In contrast to adolescent and adult men, for whom cryopreservation of semen prior to start of chemotherapy is available and widely used, there are currently no means to preserve reproductive potential in young boys diagnosed with cancer. A high percentage of male childhood cancer survivors is therefore doomed to remain childless, unless new technology is developed that allows them to fulfil their child wish. Such technology is now appearing at the horizon: cryopreservation of testicular tissue and autotransplantation of spermatogonial stem cells (SSCs).
In 1994, successful transplantation of SSCs from one mouse to another was reported (Brinster & Zimmermann, 1994). This landmark publication immediately drew attention to the fact that this method could potentially be used to preserve fertility in male cancer survivors. Since then, many groups, including centers in the Netherlands (Amsterdam UMC, location AMC and UMC Utrecht) have successfully performed SSC transplantation in various animal model systems including mouse, rat, and bovine (Creemers et al., 2002; van Pelt et al., 2002; Izadyar et al., 2003, Zhang et al., 2006, Mulder et al., 2018, Kadam et al., 2019).
In recent years, preclinical work by the group of van Pelt (Amsterdam UMC, location AMC, Amsterdam) has shown that cryopreservation and propagation of human SSCs from testicular biopsies of adult human males is possible (Sadri-Ardekani et al., 2009). Following this study, the same group has also shown proof of principle, to a certain extent, of human pre-pubertal SSCs propagation in vitro (Sadri-Ardekani et al., 2011). Many other research groups are also focussed on creating efficient SSC propagation techniques with an attempt at getting closer to the possibility of clinical application within the next few years (Hou et al., 2015, Guo et al., 2015, Dong et al., 2019). One of the main limitations of these studies is the lack of consensus on informative

human SSC markers. Therefore, more recent studies are aimed towards generating robust candidate markers for identifying and characterising human SSCs against other cell types within the testes (Guo et al., 2018, Sohni et al., 2019). This will be significantly beneficial in isolating and propagating human pre-pubertal SSCs with increased efficacy in comparison to the current available method (Sadri-Ardekani et al., 2011).
Therefore, in the group of children who are treated with chemotherapy and/or radiotherapy with high risk of infertility, affecting spermatogenesis permanently, it is important to start cryopreservation of testicular tissue now to be able to transplant SCCs later in life, which may well be more than 15 years after the cancer treatment.
Our request is in line with international activities. Ethical approval for collection of testicular material was already approved in Amsterdam UMC, location AMC (Project NL 27690.000.09 which was active from September 2009 till September 2018) the Netherlands has already been approved for children. Also in other countries such as Belgium (Vrije Universiteit Brussels, Centrum voor Reproductieve Geneeskunde (www.brusselsivf.be / prof.dr. Herman Torunaye) and the Katholieke Universiteit Leuven (Wyns et al, 2008;Wyns et al, 2007 / prof.dr. Christine Wyns) and Sweden (Karolinska Institute / Keros et al., 2007 / prof.dr. Outi Hovatta) the procedure is in place for the group of young boys of who we expect high risk of infertility. We feel it is important to now also offer young boys diagnosed with cancer in our centralized paediatric oncology center, the Princess Maxima Center in Utrecht in the Netherlands the possibility to store testicular tissue for possible future SSC autotransplantation.

Study objective

1. To preserve testicular tissue of young boys with cancer with high risk of infertility for possible autologous transplantation in the future if infertility has become apparent, and to identify germcells in the testicular tissue.
2. To gain insight in the molecular profile of isolated testicular cell fractions, including SSCs and supportive cells, before and after propagation in vitro to develop the most optimal and safe standard operation protocol for SSC isolation and in vitro propagation.
3. To follow up the unique cohort of testicular biopsied prepubertal boys (AMC, Amsterdam) diagnosed with cancer on testicular damage by determining size (ultrasound), hormonal profiles and pubertal progression and if possible semen analysis during their yearly visit to the outpatient clinic. This procedure will also be applied to the prospective cohort.

Young boys defined as Tanner stage lower or equal to P3G3 testes volume < 16 cc (diagnosed with cancer at the Princess Maxima Center Utrecht who are scheduled to undergo therapy that is predicted to have a high risk for infertility are eligible for the study if unable to produce semen containing spermatozoa of adequate quality by masturbation or electrostimulation. At our hospital, the

boys and parents are given an individual estimate on the probability of infertility in relation to their scheduled treatment and estimated risk for relapse. In addition, they will be informed about the procedure necessary to obtain testicular tissue and the possible side-effects. It is then up to the parents and patient to decide whether or not they want to proceed with storing testicular tissue. Based on our previous investigations, the majority of parents are willing for their son to undergo a testis biopsy for possible SSC autotransplantation in the future (van den Berg et al, 2007, Gajjar et al., 2015).
Follow-up cohort: The young boys from the above prospective cohort and the boys of the previous cohort (CCMO NL 27690.000.09) who are still alive will receive an informed consent if they would like to participate in the follow up project, to identify possible damage as result of the biopsy. At visit to the clinic, pubertal stage will be assessed, together with measurements of height, weight, sitting height, and parental heights. The growth chart will be reconstructed and bone age will be assessed. Laboratory evaluation will include measurements of LH, FSH, testosterone, AMH and Inhibin B concentrations ultrasound to look at defects of the testes and the volume, and if possible semen analysis.

Study design

1)To preserve testicular tissue of young boys with cancer and high risk for infertility

.2) Long term follow up of the total cohort prepuberal boys who have undergone a testicular biopsy. (AUMC NL 27690,000.09 + new cohort)

Study burden and risks

Under general anaesthesia a testicular biopsy will be taken; provided that a signed informed consent is obtained from both parents. Scheduling the testicular biopsy at the moment of performing pre-treatment procedures (such as placement of a long term tunneled catheter) minimizes the burden for the patient and will not postpone start of therapy. To minimize the risk of the biopsy, the procedure will only be done on one testis under the condition that there is no history of testicular torsion or cryptorchidism. The biopsy will be approximately 0.6-0.8 ml in size and will never exceed 30% of one testis. The technique will ensure that substantial loss of testicular tissue does not occur. Complication rate is extremely low. a hematoma or infection can occur but is mild and in most cases does not lead to postponement of treatment. Follow-up will be done at the moment of follow-up for the malignancy. No additional hospital visits are foreseen in conjunction with this proposal.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

-Young patients with malignancies treated with alkylating agents (CED >4000mg/m2), brain tumours treated with cranio-(spinal) irradiation and alkylating agents, total body irradiation, pelvic irradiation, testicular irradiation, and conditioning for stem cell transplantation. The boys and parents will be given an individual estimate on the probability of infertility in relation to their scheduled treatment.

-Only if parents/legal guardians have signed consent. And in case boys > 12 years informed consent will be signed together with the informed consent of their parents

-For follow up all boys included in the previous cohort at the Amsterdam UMC, location AMC who have undergone a testicular biopsy prior to start of chemotherapy during the period 2011-2018.

Exclusion criteria

Malignancies located in the testis, history of bilateral cryptorchidism or testicular torsion, ability to ejaculate vital spermatozoa on masturbation or electro-stimulated ejaculation. Previous history or increased risk for pre-existing (congenital) gonadal insufficiency or known chromosomal abnormalities that affect male fertility.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-10-2021
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	07-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	07-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	23-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	NL 9244
CCMO	NL73818.000.21