Testicular Biopsies in Young Boys Diagnosed with Cancer To Cryopreserve Future Fertility; Towards a Safe and Feasible Future Autologous Cell Therapy

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22319

Source
NTR

Brief title
PRINCE

Health condition

Cancer in children (Haemotooncologic, solid tumors and brain tumors)

Sponsors and support

Primary sponsor: Prinses Maxima Center for paediatric oncology and stichting bergh in het zadel
Source(s) of monetary or material Support: Prinses Maxima Center for paediatric oncology and stichting bergh in het zadel

Intervention

Outcome measures

Primary outcome

The main endpoint will be successful sampling and storage of testicular tissue (that is 75% of the samples to be stored for future stem cell preservation will have germ cells). This can be identified based on histological analyses (immuno-), possibly supported by flowcytometry and single cell sequencing. We aim to prospectively collect testicular material of all young boys with high risk of infertility that provide informed consent in our clinic. We aim to achieve 75% of the samples to be stored for future stem cell preservation to have germ cells. Around 20 male prepubertal boys will fulfill the criteria yearly. We expect 75% patients to give consent and we expect 75% to achieve the main end point. The study will start Q2 2021 and yearly we expect to include 15 patients During the total study period we hope to include 75-80 patients (total study duration 5 years)

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), and optional post-pubertal fertility (as determined by semen analysis) Striving to follow up 75% of the total cohort. Total cohort of the previous research study (research project NL 27690.000.09) total of 94 children of whom 80 are still alive. Inclusion of 75% of these children/adults will be around 60 patients who we will follow 1x year x 5 years (2021-2026) . The prospective group will also be followed 1xyear till 2026.

Study description

Background summary

Modern cancer treatment allows the majority of young boys to survive their malignancy. Unfortunately, there is a group of boys treated with high dose chemotherapy who will become infertile or have a high risk of infertility (Kenney et al., 2018, Green et al., 2014). Currently, in young boys diagnosed with cancer there are no standard means to preserve their reproductive potential, which contrasts with adolescents and adults, for whom cryopreservation of semen prior to the start of chemotherapy is available and widely used. The Amsterdam academic medical centre (research project NL 27690.000.09) has pioneered cryopreservation of testicular tissue and subsequent autotransplantation of spermatogonial stem cells (SSCs) in animal models (Izadyar et al, 2003) and has succeeded in cryopreserving and propagating human SSCs from adult men (Galdon et al., 2016). It is estimated that SSC autotransplantation can be applied clinically within the next decade. Given the long-time interval between cryopreserving testicular tissue in young boys and the possible moment of using this this tissue for autotransplantation many years later (it may be > 10 years between having childhood cancer and being diagnosed with infertility as an adult) it is necessary to continue this research and 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.
The international guidelines on risk of infertility in young boys with cancer (Mulder et al 2020,

accepted Lancet oncology) recommend us to cryopreserve testicular tissue of these young boys with high risk of infertility due to their cancer. A unique cohort has been cryopreserved in research setting at the Amsterdam UMC, location AMC Amsterdam (research project NL 27690.000.09) and doing this procedure has been proven safe (Uijldert et al., 2017).

Objectives
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.
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 size (ultrasound), hormonal profiles (including inhibin) and pubertal progression during their yearly visit to the outpatient clinic. This procedure will also be applied to the prospective cohort

Study design
objectives 1, 2 and 3: Prospective cohort study in young boys diagnosed with cancer who are predicted to have a high risk for infertility.
additional for objective 3; Follow up of the patients who were included in project Nl 27690.000.09 at the outpatient late effect clinic.
Study population
Prospective cohort:
1. Young boys (defined as Tanner stage lower or equal to P2G2 testes volume < 10 cc) diagnosed with cancer at the Princess Maxima Center who will be at high risk for infertility because of their treatment (n=20 yearly) (that is; High dose alkylating agents Cyclophosphamide equivalent dose > 4000 mg/m2, radiotherapy to the testis region, and High dose chemotherapy stem cell transplantation). (see Flow chart Recommendations for fertility preservation for male childhood, adolescent and young adult cancer patients: a report from the PanCareLIFE consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group, accepted Lancet Oncology 2020 appendix 1)
2. Follow-up cohort (research project NL 27690.000.09): follow up of all patients alive included in project NL 27690.000.09 who are now seen at regular follow up late effects clinic and will be screened using testicular ultrasound, serum hormonal profiles and pubertal progression (n=80) .
Intervention
Young boys suffering from a malignancy with high risk of infertility will undergo a testicular biopsy pre start of therapy for their cancer. This procedure will be performed during one of the general anaesthesia sessions prior to the start of chemotherapy; e.g. taking of biopsies from their tumour, biopsies from potential sites of metastatic spread, diagnostic and therapeutic lumbar punctures, insertion of (permanent) intravenous catheters. Testicular biopsies will be subjected to mechanical dissection to obtain small pieces of testicular tissue. Subsequently, these pieces will be cryopreserved and stored in a nitrogen vapour freezer under GMP conditions. 85% of the tissue will be stored for the clinic, 15% of the tissue will be used for research.

Main study parameters/endpoints
The main endpoint will be successful sampling and storage of testicular tissue (that is 75% of the samples to be stored for future stem cell preservation will have germ cells). This will be identified based on histological analyses (immuno-), possibly supported by flowcytometry and single cell sequencing. We aim to prospectively collect testicular material of all young boys with high risk of infertility that provide informed consent in our clinic. We aim to achieve 75% of the samples to be stored for future stem cell preservation to have germ cells. Around 20 male prepubertal boys will fulfill the criteria yearly. We expect 75% patients to give consent and we expect 75% to achieve the main end point. The study will start Q2 2021 and yearly we expect to include 15 patients During the total study period we hope to include 75-80 patients (total study duration 5 years).
Secondary endpoint will be 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). Striving to follow at least 75% of the total cohort . Total cohort of the previous research study (research project NL 27690.000.09) total of 94 children of whom 80 are still alive. Inclusion of 75% of these children/adults will be around 60 patients who we will follow 1x year x 5 years (2021-2026) . The prospective group will also be followed 1xyear till 2026.

Study objective

The main endpoint will be successful sampling and storage of testicular tissue (that is 75% of the samples to be stored for future stem cell preservation will have germ cells). This can be identified based on histological analyses (immuno-), possibly supported by flowcytometry and single cell sequencing. We aim to prospectively collect testicular material of all young boys with high risk of infertility that provide informed consent in our clinic. We aim to achieve 75% of the samples to be stored for future stem cell preservation to have germ cells. Around 20 male prepubertal boys will fulfill the criteria yearly. We expect 75% patients to give consent and we expect 75% to achieve the main end point. The study will start Q2 2021 and yearly we expect to include 15 patients During the total study period we hope to include 75-80 patients (total study duration 5 years)

Study design

Before start chemotherapy (physical examination, bloods, sonar of testis and planning surgical biopsy) and then yearly Follow up x 5 years (pubertal stage, bloods and length and height)

Intervention

Objective 1 and 2; Selection of the testis to be biopsied
Depending on the age of the boy and his actual sexual development testicular size will vary. To determine size, shape, consistency and texture of both testes we will do a scrotal ultrasound together with manual palpation with an orchidometer. Based on the results of these tests we will choose which testis is best suited for biopsy. Given the anticipated heterogeneity among the included patients, it is difficult to provide age-related cut-off criteria for performing a biopsy or not. We will use the volume of the testis instead (see 3.2) We will

exclude patients with testicular torsion or cryptorchidism in their history to be absolutely sure that a good functioning untouched contralateral testis will remain after the procedure.

Size of Biopsy
Ultrasonographic testis volume at birth through the age of eight is approximately 0.8 - 1.2 ml and then increases to 1.6 ml, 2.3 ml and 7.2 ml at the age of 9, 10/11 and 12/13, respectively (Beres et al, 1989). The biopsy to be taken from young boys will be approximately 0.6-0.8 ml in size with the restriction that we will never remove >30 % of one testis. We will ask the patient and/or his parents to donate a small part of this testicular biopsy (15%) for further research into fertility restoration methods based on spermatogonial stem cells. Rest 85% of the biopsy material will be stored for future use, which is also in line with the previous CCMO research project NL 27690.000.09.

Surgical procedure of testis biopsy
During general anaesthesia necessary for procedures such as implantation of a central line or bone marrow aspiration, we will perform an adapted open testicular biopsy as currently performed in adult azoospermic men in TESE procedures in our clinics. This technique combines maximal yield of SCCs with minimal damage to the testis. The procedure starts with incision of the scrotal skin, including tunica dartos, then opening of the tunica vaginalis to bring the testis outside the scrotum. After critical inspection and measurement of volume (in case of any doubts the operation can still be reversed without any harm to the testis), the tunica albuginea will be partially opened on one pole of the testis and the biopsy is taken as a wedge in such a way that the remaining tubules and rete testis will remain intact. In case of an additional TESE biopsy, the most dilated seminiferous tubules will be taken first in a separate biopsy. Meticulous coagulation of any bleeding vessels will be done by means of bipolar forceps and the tunica albuginea will be closed with absorbable single sutures (8-0). Thereafter the tunica vaginalis will be closed in a similar way and after a final control the testis will be put back to the scrotum which is also closed.
3.4 Follow up of patient after testis biopsy
During the hospital stay and at outpatient visits for malignancy, follow-up of the testicular procedure will be done by means of physical examination and ultrasound screening. Follow-up is thereby secured for 5 years after the testicular biopsy and even at a later instance at the oncological late-effects follow-up. In this Follow up programme we will also include the previous cohort. During the yearly follow-up visit, 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 and Inhibin B concentrations, and optional semen analysis will be offered.

Contacts

Public
Prinses Maxima Centrum voor Kinderoncologie
marianne van de Wetering

088-9729506
Scientific
Prinses Maxima Centrum voor Kinderoncologie
marianne van de Wetering

088-9729506

Eligibility criteria

Inclusion criteria

4.1 Population (base)
Young boys (defined as Tanner stage P2G2 testes volume < 10cc) who are diagnosed with cancer and who are scheduled to undergo treatment at high risk of infertility (that is cyclophosphamide equivalent dose (CED) of > 4000 mg/m2 or radiotherapy to volumes exposing the testes and high dose stem cell transplantation) and retrospective follow up of the previous cohort Amsterdam UMC, location AMC (102 patients).

Inclusion criteria
- Concerning objective 1 and 2; 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 signed consent.
- Concerning objective 3; All boys included in the previous cohort at the Amsterdam UMC, location AMC (research project NL 27690.000.09) who have undergone a testicular biopsy prior to start of chemotherapy during the period 2009-2018.

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. All pre pubertal boys with cancer not meeting the high risk of infertility standard

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2021
Enrollment:	80
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL9244
Other	CCMO The Hague : PMC CRC 2020-004

Study results