Multicentre prospective trial for extracranial malignant germ cell tumours including a randomized comparison of Carboplatin and Cisplatin

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This study has been transitioned to CTIS with ID 2023-507582-25-00 check the CTIS register for the current data. PRIMARY OBJECTIVESThe primary objective of MAKEI V is to assess in a randomized comparison whether the efficacy of Carboplatin (600 mg/...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON51290

Source
ToetsingOnline

Brief title
MAKEI-V

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
germ cell malignancy, Germ cell tumor

Research involving
Human

Sponsors and support

Primary sponsor: Rheinische Friedrich-Wilhelms Universität Bonn
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cancer, Childhood, Extracranial, Germ cell tumour

Outcome measures

Primary outcome

Event-free survival, defined as minimum time from the date of randomization to the following events (EFSr):

- Death from any cause

- Progressive disease, defined as increase of standard tumour marker with or without expansion of tumour mass/metastases

- Viable tumour cells at time of final surgery

- Relapse

- Second malignancy

- or the date of the last follow-up

Secondary outcome

- Event-free survival (EFS), defined as minimum time from the date of diagnosis to any of the events described above or to last follow-up, of all patients included in MAKEI V in respect to the defined MAKEI V risk groups

- Overall survival (OS), defined as minimum time from the date of diagnosis to death of any cause or to last follow-up, of all patients included in MAKEI V in respect to the defined MAKEI V risk groups

- Health economic parameter, e.g. hospitalization days during treatment, number

of blood transfusions, in respect to treatment with Carboplatin or Cisplatin

- Short and late toxicities according to CTCAE v4.03

- Assessment of safety: Adverse events and laboratory abnormalitie, CTCAE v4.03

grade, timing, seriousness and relatedness.

- Fertility relevant endocrine outcomes, e.g. Estrogen, AMH, LH, FSH, Inhibin B.

- Patient reported outcomes including HRQoL, fatigue, sexual function and

fertility outcomes (in adult patients)

- Determination of risk for relapse in respect to used surgical intervention

- Radiological response rate after two (and if applicable four) cycles of

either Carboplatin or Cisplatin chemotherapy

- Standard tumour marker levels after every cycle of either Carboplatin or

Cisplatin chemotherapy

Study description

Background summary

Malignant Germ Cell Tumours (MGCTs) are a heterogeneous disease group and may affect children, adolescents and young adults. Depending on the age at diagnosis, MGCT vary significantly with regard to their primary site, histologic diagnosis, biologic profile and clinical response to treatment. With the introduction of Cisplatin-based chemotherapy combinations in the 1970*s, overall prognosis of MGCT has dramatically improved with survival rates of up to 90% in children.

For decades cisplatin has thus been the leading agent in the treatment of MGCT. However, cisplatin is associated with potentially severe and long-lasting toxicity, which affects outcome with considerable consequences especially in young patients. In view of the very good overall prognosis in MGCT today, quality of survival has become a leading aspect in treatment design. Accordingly the current focus is on reduction of treatment burden whilst maintaining treatment efficacy. Carboplatin is known to present with a more favourable acute and long-term toxicity profile in comparison to cisplatin.

Yet, there is no definitive proof that carboplatin is not inferior to cisplatin with regard to efficacy in MGCT. Particularly in children with MGCT randomized studies addressing this issue are entirely lacking.

The MAKEI V trial examines for the first time this question for children, adolescents and female young adults suffering from MGCT within a randomized setting. In MAKEI V, four risk groups are defined based on stratification according to localization, stage, age and resection status. This risk stratification is derived from the results of the preceding study MAKEI 96 and published data. MAKEI V patients with intermediate, high and very high risk will be randomized to receive either carboplatin or cisplatin-based combination chemotherapy as the primary objective in a non-inferiority statistical design with event-free survival as the primary end point. Outcome in the low risk groups will be analysed within the secondary objectives.

Study objective

This study has been transitioned to CTIS with ID 2023-507582-25-00 check the CTIS register for the current data.

PRIMARY OBJECTIVES
The primary objective of MAKEI V is to assess in a randomized comparison whether the efficacy of Carboplatin (600 mg/m² per cycle) (AUC 7.9 mg/ml/min.) is not inferior to Cisplatin (100 mg/m² per cycle) in malignant GCT (MGCT) of intermediate, high and very high risk with regard to Event-free survival (EFSr).

SECONDARY- AND EXPLORATIVE OBJECTIVES
- Evaluation of EFS/OS-rates in the defined risk-groups compared to results of preceding consecutive trials (MAKEI 96) and published data.
- Evaluation of toxicity under treatment with Carbo- or Cisplatin patients in respect to numbers of days in hospital and numbers of applied transfusions of platelets and red blood cells
- Evaluation of toxicity during and after treatment with Carboplatin or Cisplatin in randomized patients with respect to ototoxicity, nephrotoxicity, cardiotoxicity and fertility relevant endocrine outcomes.
- Evaluation of patient-reported-outcomes (PROs) including HRQoL, fatigue, sexual function and subjective fertility outcome (in adult patients)
- Implementation of standardized documentation of surgical procedures and evaluation of potential impact of variations in procedures on EFS.
- Evaluation of risk stratification for therapy implemented in MAKEI V based on standardized staging and pathological evaluation in comparison to MAKEI 96
- Evaluation of radiological response after two (and if applicable four) cycles of either Carboplatin or Cisplatin chemotherapy.
- Evaluation of standard tumour marker kinetics after every cycle of either Carboplatin or Cisplatin Chemotherapy
- Correlation of miRNA levels with standard tumour marker levels and outcome
- Establishment of a biomaterial bank for tumour tissue and blood samples to

support biological studies of MGCT.

Study design

Prospective, multicentre phase III-trial in malignant extracranial germ cell tumours including a randomization between Carboplatin- and Cisplatin-combination standard chemotherapy based on a risk-stratification derived from the preceding MAKEI 96 trial and published data

Intervention

Randomised treatment of participants with intermediate, high, or very high risk disease with standard cisplatin (100 mg/m2 per cycle) or carboplatin (600 mg/m2 per cycle)

Study burden and risks

This protocol treatment with the cisplatin is also the standard treatment for patients with this disease. All modifications are intended to show that Cisplatin can be exchanged for Carboplatin aiming to reduce treatment burden and decrease treatment related side effects without influence on the outcome. Parents and participants are asked to fill in questionnaires at 4 time points. This takes about 20-30 minutes each time. The burden of blood sampling is negligible compared to standard care.

The potential risks of MAKEI V are:
- the possibility that Carboplatin is inferior to Cisplatin with regard to EFS in the randomized risk groups.
- that the toxicity profile of Carboplatin displays higher myelotoxicity in comparison to Cisplatin with the need for blood transfusions harboring risks of transmitting infections and leading to prolongation of hospital visit.
- that the treatment intensification for very high risk patients leads to a higher rate of death of complications

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

- Confirmed extracranial MGCT up to 17 11/12 years of age or patients with ovarian primaries up to 29 11/12 years of age on the date of written informed consent.
- Diagnosis of a chemotherapy-naïve extracranial MGCT
- Written informed consent of patients and/or their parents according to national law prior to trial entry
- Karnofsky-Index of >70% or ECOG-Status 0-II
- Negative pregnancy test within 7 days prior to starting treatment for female patients of childbearing potential, in case of ß-HCG secreting MGCT pregnancy has to be excluded by appropriate methods

Exclusion criteria

- Pregnancy
- Lactation
- Incomplete data at trial entry preventing risk group allocation
- HIV-positivity
- Live vaccine immunization within two weeks before start of protocol treatment
- Sexually active adolescents not willing to use highly effective contraceptive

method (pearl index <1)
until 12 months after end of chemotherapy
- Current or recent (within 30 days prior to date of informed written consent) treatment with another investigational drug or participation in another interventional clinical trial, except trials with different end points than MAKEI V that can run in parallel to MAKEI V without influencing that trial
- Any other medical, psychiatric or drug related condition, or social condition incompatible with protocol treatment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-02-2024
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cisplatin

Generic name:	Cisplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Etoposide
Generic name:	Etoposide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ifosfamide
Generic name:	Ifosfamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-11-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-03-2023
Application type:	First submission
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-507582-25-00
Other	DRKS00019921
EudraCT	EUCTR2016-001784-36-NL
CCMO	NL81795.041.22