An international prospective umbrella trial for children with atypical teratoid/rhabdoid tumours (ATRT) including
A randomized phase III study evaluating the non-inferiority of three courses of high-dose chemotherapy (HDCT) compared to focal radiotherapy as consolidation therapy

Published: 14-04-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2022-501456-28-00 check the CTIS register for the current data. Primary objectives Part A:To test the non-inferiority, as evaluated by OS, of three courses of HDCT compared to focal RT plus...

Ethical review	Approved WMO
Status	Pending
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON51928

Source
ToetsingOnline

Brief title
ATRT01

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
atypical teratoid/rhabdoid tumours; brain tumours

Research involving
Human

Sponsors and support

Primary sponsor: German Paediatric Oncology Group, GPOH gGmbH
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: atypical teratoid/rhabdoid tumours, Paediatric, Phase III, Umbrella study

Outcome measures

Primary outcome

Primary endpoint for all parts: Overall survival (2-year follow-up, for Part A

non-inferiority of the HDCT arm)

Secondary outcome

Secondary endpoints specific for Part A = randomized trial:

-Test the non-inferiority, as evaluated by OS (5-year follow-up), of three

courses of HDCT compared to focal RT plus conventional chemotherapy

-Compare the neurocognitive outcome in the two treatment arms before

randomization, 2 and 5 years after randomization, including demonstration and

quantification of the superiority of neuropsychological performance in children

and adolescents with ATRT following treatment by HDCT, compared to those

treated with RT; identification of risk factors for differences in outcome

-Compare the quality of life in the two treatment arms before randomization, 2

and 5 years following randomization

-Compare event-free survival (EFS), progression-free survival (PFS) and OS between arms and to historical controls

-Compare the incidence and severity of Adverse Events (AEs) in each of the arms

-Compare the incidence and severity of late effects in each of the arms

-Assess the response to induction chemotherapy and compare it with that of historical controls.

Secondary endpoint specific for Part B:

-Assess the efficacy, as evaluated by OS (5-year follow-up), of three courses of HDCT as a consolidation measure following conventional-type chemotherapy in children with ATRT aged <12 months at the time of HDCT and not eligible for randomization in Part A of this protocol, compared to historical controls.

Secondary endpoint specific for Part C:

-Assess the efficacy, as evaluated by OS (5-year follow-up), of RT as a consolidation measure combined with conventional-type chemotherapy in children aged >=36 months with ATRT and not eligible

Secondary endpoints (Parts B and C):

-Assess the neurocognitive outcome in the cohorts following induction at diagnosis, 2 and 5 years after diagnosis

-Assess the quality of life in the cohort following induction at diagnosis, 2 and 5 years after diagnosis

-Compare EFS and PFS to that of historical controls

-Assess the incidence and severity of AEs

-Assess the incidence and severity of late effects

-Assess the response to induction chemotherapy and compare it with that of historical controls.

Exploratory/Teritary endpoints (all Parts):

-Identify and describe new clinical and biological risk factors in children with ATRT

-Explore the relationship between molecular subgroups as assessed by 850k methylation array and clinical characteristics

-Evaluate the feasibility of reference evaluation (imaging and pathology, molecular genetics, cerebrospinal fluid (CSF) and biological specimen collection for all enrolled patients

-Detect, quantify and identify risk factors for increased cognitive sequelae over time following treatment among patients in the three parts of the study

-Compare the cognitive functions of children to the results of patients with other central nervous system (CNS) tumour entities.

Study description

Background summary

Intracranial rhabdoid tumours (ATRT) are a rare and clinically rather challenging entity. Survival rates have remained poor despite aggressive multimodal treatment approaches. Controlled clinical trials are scarce and difficult to perform due to ATRT infrequency and presence mainly in very young

children.
As over 70% of patients with ATRT are diagnosed before 3 years of age the current trial targets this highly vulnerable population, to evaluate whether three courses of HDCT are non-inferior to radiotherapy in terms of 2- and 5-year overall survival (primary endpoint).

Although evidence and studies on late-effects of paediatric brain tumours are well established and monitoring neuropsychological and QoS aspects in paediatric brain tumour trials is to be accepted as state-of-the-art, knowledge on neuropsychological sequelae and the impact on QoS in patients with ATRT are still scarce.
The lack of specific studies on late-effects in this group is even more crucial, when considering that young age at the time of treatment for brain tumours treated with radiotherapy is associated with increased cognitive sequelae.

As survival rates in increase, the question of neuropsychological late-effects and questions of QoS need to be taken into account for the development of further medical treatments and are necessary for a better understanding of the needs of affected patients regarding participation and reintegration following treatment. Thus, it is important to compare cognitive sequelae and late-effects in affected patients treated with RT versus patients treated with HDCT according to the present protocol. Additionally, it is important to validate the commonly known
risk factors for late-effects in paediatric brain tumour patients for the ATRT-cohort.

In summary, the following essential scientific research questions remain open:
1) Is HDCT inferior to conventional type chemotherapy with focal RT in terms of 2- and 5-year overall survival in young children with ATRT?
2) Can young children with ATRT survive with a markedly better neurocognitive outcome if focal RT is replaced by three courses of HDCT?

Study objective

This study has been transitioned to CTIS with ID 2022-501456-28-00 check the CTIS register for the current data.

Primary objectives Part A:
To test the non-inferiority, as evaluated by OS, of three courses of HDCT compared to focal RT plus conventional chemotherapy as consolidation therapy following conventional chemotherapy in children with ATRT aged 12 - 35 months at consolidation therapy.

Primary objectives Part B:
To assess the efficacy, as evaluated by OS, of three courses of HDCT as a consolidation measure following conventional-type chemotherapy in children with

ATRT aged <12 months at the time of HDCT and not eligible for randomization within Part A of this protocol, compared to historical controls.

Primary objectives Part C:
To assess the efficacy, as evaluated by overall survival, of RT as a consolidation measure combined with conventional-type chemotherapy in children aged >=36 months with ATRT, compared to historical controls.

Secondary objectives Part A:
a) To test the non-inferiority, as evaluated by OS (5-year follow-up), of three courses of HDCT compared to focal RT plus conventional chemotherapy
b) Compare the neurocognitive outcome in the two treatment arms before randomization, 2 and 5 years after randomization, including (b1) demonstrating and quantifying the superiority of neuropsychological performance in children and adolescents with ATRT following treatment by
HDCT, compared to those treated with RT, (b2) identifying risk factors for differences in outcome
c) Compare the QOL in the two treatment arms before randomization, 2 and 5 years after randomization
d) Compare EFS, PFS and OS between arms and to historical controls
e) Compare the incidence and severity of AEs in each of the arms
f) Compare the incidence and severity of late effects in each of the arms
g) Assess the response to induction chemotherapy and compare it with that of historical controls.

Secondary objectives Part B:
a) Assess the efficacy, as evaluated by OS (5-year follow-up), of three courses of HDCT as a consolidation measure following conventional-type chemotherapy in children with ATRT aged <36 months at the time of HDCT and not eligible for randomization in Part A of this protocol, compared
to historical controls
b) Assess the neurocognitive outcome at diagnosis, 2 and 5 years after diagnosis in cohort
c) Assess the quality of life at diagnosis, 2 and 5 years after diagnosis in the cohort
d) Compare EFS and PFS to that of historical controls
e) Assess the incidence and severity of AEs
f) Assess the incidence and severity of late effects
g) Assess the response to induction chemotherapy and compare it with that of historical controls.

Secondary objectives Part C:
a) Assess the efficacy, as evaluated by OS (5-year follow-up), of RT as a consolidation measure combined with conventional-type chemotherapy in children aged >=36 months with ATRT, compared to historical controls
b) Assess the neurocognitive outcome at diagnosis, 2 and 5 years after

diagnosis in cohort
c) Assess the QOL at diagnosis, 2 and 5 years after diagnosis in the cohort
d) Compare EFS and PFS to that of historical controls
e) Assess the incidence and severity of AEs
f) Assess the incidence and severity of late effects
g) Assess the response to induction chemotherapy and compare it with that of historical controls.

Study design

Prospective, open label multicentre, international, umbrella trial including a randomized phase III study evaluating the non-inferiority of 3 courses of high-dose chemotherapy compared to focal radiotherapy plus standard chemotherapy as a consolidation measure following conventional chemotherapy in children with ATRT ranging from 12 - 35 months at the time of consolidation (RT vs. HDCT).

Intervention

Part A: Patients will be allocated in a 1:1 ratio to each arm: HDCT arm versus RT arm

Part B: HDCT

Part C: RT

Study burden and risks

This study compares two SoC therapies (HDCT versus RT), which the patients would have received outside of the study as well.

Contacts

Public
German Paediatric Oncology Group, GPOH gGmbH

Chausseestr. 128/129
Berlijn 10115
DE
Scientific
German Paediatric Oncology Group, GPOH gGmbH

Chausseestr. 128/129
Berlijn 10115

DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Umbrella trial:
1. Age at diagnosis from birth to 18 years
2. Pathology compatible with ATRT and INI1 loss or SMARCB1 or SMARCA4 deficiency confirmed by local pathology lab
3. Written informed consent and/or assent for study participation according to national legislation
4. Patient agrees to use effective contraception whilst on treatment (patients of childbearing potential)

Part A:
1. Enrolled in the umbrella trial
2. Received 3 courses of induction chemotherapy according to protocol and following induction in SD or better
3. Expected age 12-35 months at time of consolidation therapy (RT or HDCT)
4. Written informed consent and/or assent for randomization according to national legislation
5. Central review of pathology confirmed ATRT
6. MRI (magnetic resonance imaging) and CSF examination after 3 courses of chemotherapy and, if applicable, later showing SD or better (central review - national or regional centre)
7. Alanine transaminase (ALT) or aspartate transaminase (AST) <=3.0 x upper limit of normal (ULN) and bilirubin <=1.5 x ULN
8. Creatinine <= 1.5 x ULN and measured glomerular filtration rate (GFR) defined

age-related values according to national standard methods.
9. Ejection fraction (EF) >=50% or fractional shortening (FS) >=29% by echocardiography

Part B:
1. Enrolled in the umbrella trial
2. Received 3 courses of induction chemotherapy according to the protocol
3. Radiotherapy not admissible (e.g. <12 months or other contraindications)
4. Not eligible for the randomized trial (Part A) (e.g. refusal of randomization)
5. Written informed consent and/or assent for inclusion according to national legislation
6. Central review of pathology confirmed ATRT
7. MRI and cerebrospinal fluid examination after 3 courses of chemotherapy and, if applicable, later showing clinically significant sensitivity to chemotherapy (central review - national or regional centre)
8. ALT or AST <=3.0 x ULN, bilirubin <= 1.5 x ULN
9. Creatinine <= 1.5 x ULN and measured GFR within published defined age-related values according to national standard methods
10. EF >=50% or FS >=29% by echocardiography.

Part C:
1. Enrolled in the umbrella trial
2. Received 3 courses of induction chemotherapy according to the protocol
3. Aged 36 months or above OR
4. HDCT not possible OR
5. Not eligible for the randomized trial (Part A)
6. Written informed consent and/or assent for inclusion according to national legislation
7. Central review of pathology confirmed ATRT
8. MRI and CSF examination after 3 courses of chemotherapy and, if applicable, later showing SD or better (central review - national or regional centre)
9. ALT or AST <=3.0 x ULN, bilirubin <= 1.5 x ULN
10. Creatinine <= 1.5 x ULN and measured GFR within published defined age-related values according to national standard methods.
11. EF >=50% or FS >=29% by echocardiography

Exclusion criteria

Part A:
1. Previous or concomitant tumour directed chemotherapy, RT or targeted therapy, other than within the SIOPE ATRT01 trial
2. Metastatic disease at primary diagnosis
3. At time of inclusion Diarrhoea grade 3 or worse according to the CTCAE v5.0, if uncontrolled despite optimal supportive therapy

4. History or presence of clinically significant cardiac disease, including, but not limited to, any of the following, if uncontrolled despite optimal supportive care:
a. Sustained ventricular tachyarrhythmia
b. Any ventricular fibrillation or torsade de pointes,
5. At time of inclusion bradycardia defined as persistent heart rate < 50/minute if uncontrolled despite optimal supportive therapy. Screening electrocardiogram (ECG) with a QT corrected by Bazett*s (QTcB) >450msec minute if uncontrolled despite optimal supportive therapy
6. Pulmonary hypertension as diagnosed by a paediatric cardiologist with indirect (echocardiography) or direct signs (pulmonary artery pressure >=25mmHg)
7. Any contraindication to any planned chemotherapy drug according to summary of medical product chart (SmPC)
8. Known active hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunedeficiency virus (HIV) infection
9. Participation in another interventional therapeutic clinical trial
10. Patients on coumarin-derivative anticoagulants
11. History of thrombosis or sinusoidal obstruction syndrome (SOS)
12. Any ongoing, uncontrolled, clinically significant infection (viral, bacterial or fungal)
13. Neutropenia (absolute neutrophil count (ANC) <0.5 x109/L) lasting 6 weeks from the start of the previous course of chemotherapy
14. Synchronous multifocal rhabdoid tumours
15. Hypersensitivity to the active compounds or other excipients contained in one of the investigational medical products listed in the SmPC.

Part B:
1. Previous or concomitant tumour directed chemotherapy, radiotherapy or small molecule therapy, other than within the SIOPE ATRT01 trial
2. At time of inclusion Diarrhoea grade 3 or worse according to the CTCAE v5.0, if uncontrolled despite optimal supportive therapy
3. History or presence of clinically significant cardiac disease, including, but not limited to, any of the following, if uncontrolled despite optimal supportive therapy:
a. Sustained ventricular tachyarrhythmia
b. Any ventricular fibrillation or torsade de pointes
c. Current bradycardia defined as heart rate < 50/minute
d. Screening ECG with a QTcB >450msec
4. Pulmonary hypertension as diagnosed by a paediatric cardiologist with indirect (echocardiography) or direct signs (pulmonary artery pressure >=25mmHg)
5. Any contraindication to any planned chemotherapy drug according to SmPC
6. Known active HBV, HCV or HIV infection
7. Participation in another interventional therapeutic clinical trial
8. Patients on coumarin-derivative anticoagulants
9. History of thrombosis or SOS
10. Any ongoing, uncontrolled, clinically significant infection (viral, bacterial or fungal)

11. Neutropenia (ANC <0.5 x109/L) lasting 6 weeks from the start of the previous course of chemotherapy
12. Hypersensitivity to the active substance or other excipients contained in one of the investigational medical products listed in the SmPC.

Part C:
1. Previous or concomitant tumour directed chemotherapy, RT or small molecule therapy, other than within the SIOPE ATRT01 trial
2. Any contraindication to any planned chemotherapy drug according to SmPC
3. Participation in another interventional therapeutic clinical trial
4. Any ongoing, uncontrolled, clinically significant infection (viral, bacterial or fungal)
5. Hypersensitivity to the active substance or other excipients contained in one of the investigational medical products listed in the SmPC.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2022
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin

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

Ethics review

Approved WMO Date:	14-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-07-2022
Application type:	First submission
Review commission:	METC NedMec (Utrecht)

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	CTIS2022-501456-28-00
EudraCT	EUCTR2018-003335-29-NL
CCMO	NL78097.041.22