AN INTERNATIONAL PROSPECTIVE TRIAL ON HIGHRISK MEDULLOBLASTOMA IN PATIENTS OLDER THAN 3 YEARS

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This study has been transitioned to CTIS with ID 2024-510578-25-00 check the CTIS register for the current data. Primary objectives:- To evaluate whether the outcome in children, young people and adults with HR-MB is improved over standard therapy i...

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

Summary

ID

NL-OMON54193

Source
ToetsingOnline

Brief title
SIOP HR-MB

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
brain tumour, medulloblastoma

Research involving
Human

Sponsors and support

Primary sponsor: University of Birmingham
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: (quality of) survival, children, High-risk medulloblastoma, treatment

Outcome measures

Primary outcome

The primary outcome measure is event-free survival (EFS).

Secondary outcome

Secondary: Overall survival (OS), progression free survival (PFS), toxicity

(including late

effects), Quality of Survival (QoS).

Study description

Background summary

Medulloblastoma (MB) is the most common malignant brain tumour in children and young people,
accounting for approximately 650 new cases per year in the European Union (EU). These tumours of the posterior fossa account for 20% of all brain tumours in children. The median age of diagnosis is 7 years, but medulloblastoma occurs at all ages and into adulthood.
MB can be defined according to histological and genetic subtypes. Our understanding of these variants, and their clinical relevance is evolving and altering our understanding of prognosis and risk and are creating a shifting scope of disease stratification. However, the challenge of high -risk medulloblastoma (HRMB) remains predominantly a clinical one and the same dichotomy of improving survival rates and reducing toxicity and late effects remains.
Around 30% of MB patients are diagnosed as HR-MB; currently defined clinically by the presence of
one or more of the following high-risk factors; metastatic disease, large cell/anaplastic histology, MYC or MYCN amplification or significant residual disease post-surgery. HR-MB is associated with a 5-year event-free survival (EFS) of about 60%. Moreover, those patients that are cured have significant long-term toxicities (including neurocognitive and endocrinological).
Initial studies indicate the severity of toxicity and late-effects may be associated with treatment given, clinico-biological disease features, and host

genetic factors. There is therefore an urgent need to improve survival in patients with HR-MB, whilst at the same time limit acute and long-term toxicities that have significant detrimental impact on the quality of life of survivors. It is also vital to undertake biological analysis of tumour samples to identify those patients currently defined as having high risk disease but have a better prognosis and may be better treated as standard risk patients and identify those patients who are unlikely to be cured by current conventional therapy, and/or in whom the evaluation of novel therapies at an earlier stage may be appropriate.

To date, there has been a worldwide paucity of large clinical trials for HR-MB to support the systematic development of optimal evidence-based treatment approaches for this disease group. The major alternative approaches to date include (i) high-dose chemotherapy prior to (or occasionally post-) craniospinal radiotherapy (RT), (ii) hyperfractionated and accelerated RT (HART; twice daily) and (iii) conventional craniospinal (RT) (once daily), most commonly prior to maintenance chemotherapy. Most importantly, the relative merits of these approaches have not been tested in a systematic way and have not taken into account the heterogeneous disease biology we now appreciate. In addition, the relative associated toxicities or late-effects of the different treatment strategies have not been assessed. A randomised multi-national trial to ascertain whether any of these strategies offers a survival advantage is needed.

Study objective

This study has been transitioned to CTIS with ID 2024-510578-25-00 check the CTIS register for the current data.

Primary objectives:
- To evaluate whether the outcome in children, young people and adults with HR-MB is improved over standard therapy i.e. conventional (once a day) radiotherapy (RT) (standard therapy), for those treated with: hyperfractionated-accelerated radiotherapy (HART), or high-dose therapy (HDT) with thiotepa followed by conventional RT.
- To evaluate whether the outcome in HR-MB is different for those treated with two different maintenance chemotherapy therapies.

Secondary objectives:
- To study the late effects of treatment and their impact on quality of survival (QoS), including
neurocognitive function, neurological impairment, endocrine impairment, audiological function and secondary tumours.
- To conduct comprehensive prospective biological studies in HR-MB, with the aims of (i) understanding the biological basis of HR-MB, (ii) identification and validation of diagnostic and prognostic biomarkers, and (iii) identification and validation of molecular targets with therapeutic potential

and associated predictive biomarkers.
- To conduct prospective QoS, toxicity and pharmacogenomic studies with the aim of exploring clinical, host and tumour factors, and genetic variants, that relate to early and late side-effects of treatment and survival parameters.

Study design

An international, prospective, phase III randomised trial in patients aged 3 years and older with *high-risk* medulloblastoma with a high-risk biological profile.
Patients eligible for the trial will be randomized for radio(chemo)therapy (R1), and maintenance chemotherapy (R2).

Intervention

Induction chemotherapy:
Carboplatin and etoposide (2 cycles of 3 weeks)

Randomization 1: radio(chemo)therapy
Arm A: conventional radiotherapy (1x/day for 6 weeks)
Arm B: Hyperfractionated-Accelerated Radiotherapy (HART; 2x/day for 23 days)
Arm C: high-dose chemotherapy with thiotepa (2 cycles of 3 weeks) followed by conventional radiotherapy (1x/day for 6 weeks)

Randomization 2: maintenance chemotherapy (applies only for arm A and B)
Arm D: 4 AB cycles. Cycle A: vincristine, lomustine, cisplatin (6 weeks); cycle B: vincristine and cyclophosphamide (3 weeks) (total of 36 weeks)
Arm E: 6 cycles of temozolomid (4 weeks) (total of 24 weeks)

Patients randomized to arm C will receive automatically 6 cycles of temozolomide (alike arm E)

Study burden and risks

Burden:
Compared to arm A:
Arm B: patients will receive radiotherapy twice a day in stead of once per day. Patients will finish radiotherapy one week earlier. Patients will not be hospitalized for radiotherapy, which is comparable to patients from arm A.
Arm C: apheresis will be conducted during induction chemotherapy. Depending on the harvest of stem cells during the first cycle, a second harvest during the second cycle of induction chemotherapy may be needed. Patients receive two high-dose chemotherapy before radiotherapy. During this high-dose chemotherapy patients will be hospitalized. The duration of hospitalization is depending on the amount of side effects. Radiotherapy is equal to arm A.

Compared to arm D:
Arm E and patients from arm C: maintenance chemotherapy will take place at home. Patients only have control visits at the hospital and have to receive the medication at the hospital. Patients will be less often hospitalized than patients from arm D.

All included patients will receive questionnaires regarding Quality of Life at different time points (max. 4 times) and neuropsychological testing at the same time points.
Independent from study arm, for patients with CSF positive for tumor cells at day 15 after surgery, CSF sampling will be repeated for 3 to 4 times (depending of study arm) during the study.

Risks:
It is unsure whether patients from arm B have a higher risk for side effects or not compared to patients receiving radiotherapy once a day.
Patients from arm C have a higher risk for infections during high-dose chemotherapy. They also have a higher risk for infertility compared to other patients in the study. All included patients will be advised regarding fertility preservation.

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)

Inclusion criteria

Inclusion criteria for trial entry and R1:
• Histologically proven (centrally reviewed) high-risk medulloblastoma, with any of the currently defined histological subtypes. High-risk disease is defined as patients with sonic hedgehog (SHH) or non-SHH/non-wingless-type (WNT) (Groups 3 and 4) medulloblastoma, with at least one of the following high risk features:
o Metastatic disease: Chang Stage M1, M2 and M3
o Large cell/anaplastic MB (as defined by World Health Organisation (WHO) criteria 2016
o Patients with MYC or MYCN amplified tumours (unless MYCN amplified non-WNT/non-SHH Group 4 without any other high risk factors)
o Patients with somatic SHH-TP53 mutant tumours .
o Patients with significant residual tumour (> 1.5 cm2) following surgical resection of the primary tumour and other biological risk factors (as above)

• Age at diagnosis >=3 years. The date of diagnosis is the date on which initial surgery is undertaken
• Submission of biological material, including fresh frozen tumour samples and blood, in accordance with national and international schemes for molecular genetic assessment of biological markers, and for associated biological studies
• No prior treatment for medulloblastoma, other than surgery, with the exception of one cycle of induction chemotherapy with carboplatin and etoposide may be given prior to trial entry and randomisation where there is clinical urgency to start treatment
• Adequate hepatic function defined as:
o Total bilirubin <= 1.5 times upper limit of normal (ULN) for age, unless the patient is known to have Gilbert*s syndrome
o ALT or AST < 2.5 X ULN for age
• Adequate renal function defined as creatinine < 1.5 x ULN
• Adequate haematological function defined as ANC >=1 x 109/L; platelets >= 100 x 109/L, prior to induction chemotherapy
• No significant hearing deficit in at least one ear (significant hearing deficit defined as Chang grade 3 or above)
• Medically fit to receive protocol treatment
• Documented negative pregnancy test for female patients of childbearing

potential
• Patient agrees to use effective contraception whilst on treatment (patients of childbearing potential)
• Written informed consent from the patient and/or parent/legal guardian

Inclusion criteria for Randomisation 2 (R2):
• Patient entered into the SIOP-HRMB trial at diagnosis
• Patient treated with:
o Either Arm A (conventional radiotherapy) or Arm B (HART)

Exclusion criteria

Exclusion criteria for trial entry and R1:
• Patients with proven or with high likelihood of germline TP53, APC, PTCH1, SUFU, PALB2, BRCA2 gene alteration or any other DNA repair defect
• Non-WNT/non-SHH Group 4 patients with MYCN amplification and no other high-risk factor
• Patients with CTNNB1 mutation positive WNT medulloblastoma irrespective of other risk factors
• Patients with significant residual tumour (> 1.5 cm2) following surgical resection of the primary tumour and no other biological risk factors
• Chang Stage M4 disease
• Brainstem or embryonal tumours in other sites
• Patients previously treated for a brain tumour or any type of malignant disease
• Medical contraindication to radiotherapy or chemotherapy
• Known hypersensitivity to any of the treatments or excipients
• Females who are pregnant or breastfeeding
• Patients who cannot be regularly followed up due to psychological, social, family, geographical or other issues
• Patients for whom non-compliance with treatment, management guidelines or monitoring is expected

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):	10-10-2022
Enrollment:	40
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Belustin
Generic name:	lomustin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cytoxan
Generic name:	Cyclophosphamid
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Paraplatin
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Platinol
Generic name:	Cisplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Toposar, e.a.
Generic name:	Etoposide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-11-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-01-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-12-2023
Application type:	Amendment
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	CTIS2024-510578-25-00
EudraCT	EUCTR2018-004250-17-NL
ISRCTN	ISRCTN:16314648

Register	ID
CCMO	NL73437.041.20