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An international study comparing a number of treatment options for patients older than three years with medulloblastoma (a type of brain cancer) and clinical or biological features that make these patients more difficult to treat (high-risk disease)

Submission date
19/08/2019

Recruitment status
Recruiting

Registration date
22/08/2019

Overall study status
Ongoing

Last Edited
10/09/2025

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-treatments-for-a-brain-tumour-called-medulloblastoma-hr-mb (added 17/03/2021)

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-004250-17, CTIS 2024-510578-25

Integrated Research Application System (IRAS)
256748

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 42202

Study information

Scientific Title
An international prospective trial on high-risk medulloblastoma in patients older than three years

Acronym
SIOP-HRMB

Study objectives
High-risk medulloblastoma still has unacceptable mortality despite biological advances. The hypothesis is that either high dose therapy prior to radiation or using a different radiotherapy strategy may improve outcome without increasing long term effects of treatment. It is also hypothesised that less intense maintenance therapy may have equivalent results to the more intense therapy currently used but with less toxicity

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/10/2019, NHS HRA REC London Central (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH; +44 (0)207 104 8168; NRESCommittee.London-Central@nhs.net), ref: 19/LO/1336

Study design
Randomized; Interventional; Design type: Treatment, Drug, Radiotherapy

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Medulloblastoma

Interventions

SIOP-HRMB is an international, prospective, phase III randomised trial in patients older than the age of 3 years with 'high-risk' medulloblastoma. Following local diagnosis of HR-MB, consenting patients enter a screening phase during which time histological diagnosis will be centrally reviewed and biological investigations will be performed to confirm eligibility for the trial. Patients who meet the eligibility criteria will be offered the opportunity to take part in the trial.

Trial entry and the first randomisation will occur post-surgery before the commencement of induction chemotherapy once all inclusion criteria have been met and informed consent for trial entry and the first randomisation has been obtained. All consenting patients will receive 2 cycles of induction chemotherapy (2 x 21-day cycles of i.v carboplatin given as 160 mg/ m2 daily for days 1-5 and i.v. etoposide given as 100 mg/ m2 daily for days 1-5). Prior to the commencement of induction chemotherapy patients should have a clinical and neurological examination which will include an assessment of coordination, balance and speech, audiology test, blood tests, including full blood count, and a Quality of Survival assessment. A full blood count should be performed prior to each cycle of induction chemotherapy and preferably every 2 weeks during induction chemotherapy treatment.

Patients will be randomised to the different treatment arms taking into account clinical and biological risk factors to
ensure that these factors are balanced across the different treatment arms.

Randomisation 1
Consenting patients will be randomised at trial entry to receive one of three treatments post-induction chemotherapy. For patients in all arms, the following investigations should be performed prior to the start of radiotherapy: Clinical and neurological examination which will include an assessment of coordination, balance and speech, cranial and spinal MRI, audiology and full blood count. Blood counts should be measured at least once a week during radiotherapy.

Arm A: Conventional (once a day) RT (standard arm)
- Brain - 36Gy in 20 daily fractions
- Spine - 36 Gy in 20 daily fractions
- Primary tumour boost - 18 Gy in 10 daily fractions
- Metastatic sites boost- Brain: 18 Gy in 10 daily fractions; Spine: 9 Gy in 5 daily fractions

Arm B: Hyperfractionated and accelerated RT (HART)
- Brain - 39Gy in 30 twice-daily fractions
- Spine - 39Gy in 30 twice fractions
- Primary tumour boost - 20.8 Gy in 16 twice-daily fractions
- Metastatic sites boost- Brain: 20.8 Gy in 16 twice-daily fractions; Spine: 7.8 Gy in 6 twice-daily fractions

Arm C: High dose chemotherapy followed by conventional RT
- Patients randomised to this arm will require peripheral stem cell mobilisation and harvesting after the first and/or second course of induction chemotherapy. Prior to the commencement of treatment with high dose thiotepa, patients randomised to arm C should have a clinical and neurological examination which will include an assessment of coordination, balance and speech, dental review, blood tests, whole brain and craniospinal axis MRI, audiology test.
- High dose thiotepa (2 x 21-day cycles of i.v. thiotepa given as 200 mg/ m2 daily for 3 days followed by peripheral stem cell re-infusion 24 hours after the last dose of thiotepa. G-CSF support will commence after the stem cell reinfusion).
- Radiotherapy will be given as per Arm A
- Patients randomised to Arm C are not eligible for the second randomisation as it is felt

standard maintenance therapy will not be tolerated due to bone marrow suppression and will be treated with temozolomide maintenance chemotherapy (6 x 28-day cycles of oral temozolomide given as 150 mg/ m2 daily for 5 days).

Participation in randomisation 1 is mandatory in order to participate into randomisation 2.

Randomisation 2
Consenting patients will be randomised to receive one of two maintenance chemotherapy regimens:

Arm D: Standard maintenance therapy with Vincristine/CCNU (lomustine/Cisplatin alternating with Vincristine/cyclophosphamide
Patients randomised to this arm will receive 8 chemotherapy cycles in the order of A-B-A-B-A-B-A-B
- A (cycles 1, 3, 5, 7): IV cisplatin 70 mg/m2 day 1, oral CCNU 75 mg/m2 day 1, IV vincristine 1.5 mg /m2 (maximum 2 mg) days 1, 8 and 15
- B (cycles 2, 4, 6, 8): IV cyclophosphamide (1000 mg/m2/d days 1 and 2), IV vincristine 1.5 mg/m2 (maximum 2 mg) (day 1)
The interval after Arm A will be 6 weeks; the interval after Arm B will be 3 weeks

Arm E: Temozolomide maintenance chemotherapy
Patients randomised to this arm will be treated with temozolomide maintenance chemotherapy (6 x 28-day cycles of oral temozolomide given as 150 mg/ m2 daily for 5 days)

Prior to the commencement of maintenance chemotherapy all patients should have the following assessments: Clinical and neurological examination which will include an assessment of coordination, balance and speech, cranial and spinal MRI, audiology test, blood tests including full blood count. With the exception of the MRI and audiology assessments, these examinations should be performed before the start of each cycle of maintenance chemotherapy and a full blood count should be performed at least 2 weeks after the start of each cycle. Audiology should be performed before each cycle of chemotherapy containing cisplatin. Whole-brain MRI with and without contrast and
craniospinal axis MRI should be performed after three, six and the final cycle of maintenance chemotherapy (patients on Arm E only need the assessments at 3 cycles and at the end of treatment).

All patients on the trial will have Quality of Survival and neurocognitive assessments post-surgery and before induction chemotherapy, two years post-diagnosis, 5 years post-diagnosis and at 18 years of age.

Biological Studies
Samples of tumour tissue, blood and cerebrospinal fluid collected at diagnosis will be used for biological research studies associated with SIOP-HRMB. These studies will look for biological markers on the tumour tissue that can be used to predict the course of the disease and to see if there are any associations between the biological markers and treatment outcome.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Event-free survival (EFS). An “event” is considered to be any progression or relapse of disease, any deaths, and any occurrence of a secondary neoplasm. “Relapse” is defined as the appearance of local disease, metastasis, or both following documented complete resection, or previous complete response.“Progression” is defined as tumour growth > 25% (based on the three-dimensional measurement on the MRI) in the case of residual tumour. “Secondary neoplasm” is defined as any diagnosed neoplasm that was distinct from medulloblastoma.

Key secondary outcome(s))
1. Overall survival (OS) and progression-free survival (PFS). Measured from date of randomisation to date of death, relapse or progression for PFS or to date of death for OS; patients will be censored at date last seen if lost to follow-up.
2. Pattern of relapse. The site and time to local progression will be the measures for local tumour control. Particular attention will be given to posterior fossa relapse, i.e. local relapse within the tumour bed, or metastatic relapse to the posterior fossa outside the tumour bed. The time period begins on the date of surgery and ends on the date of appearance of relapse /progression. The appearance of metastases will not be regarded as local progression.
3. Indirect and direct measures of QoS. Both indirect and direct measures will be those agreed in the Core ‘Plus’ model. Indirect measures will use standardised, patient/parent-reported questionnaires for the measurement of: health status [Health Utilities Index 3 (HUI3)], executive function (BRIEF), behavioural outcome (Strengths and Difficulties Questionnaire (SDQ), medical, educational, employment and social situation (MEES), fatigue (Paediatric Quality of Life inventory (PedsQL) Multidimensional Fatigue Scale and, in adults, the Multidimensional Fatigue Inventory (MFI), and QoL (PedsQL Core and, in adults, the EORTC Quality of Life Questionnaire (QLQ-C30)). The timepoints for measuring QoS are at baseline, 2 years after diagnosis, 5 years after diagnosis and at age 18.
4. Audiological toxicity. The extent of ototoxicity-based dose modifications of maintenance chemotherapy, as well as the results of Pure Tone Audiometry (PTA) graded by the Chang criteria evaluated 2 years after trial entry will be the measures for audiological toxicity.
5. Endocrine function. FSH levels (cut-off level >15 IU/l) will be used as a biomarker for subfertility in post-pubertal patients. Growth retardation will be calculated as the difference in height standard deviation score (SDS) from diagnosis, and the need for, time to, and duration of hormone supplementation will be used as surrogate markers for endocrine deficits. All measures will be evaluated 2 and 5 years from trial entry and again in adulthood at 18 years.
6. Neurological function. The occurrence and severity of posterior fossa syndrome (as measured by the cerebellar mutism syndrome survey at trial entry), and the occurrence and severity of persisting cerebellar symptoms (measured by the brief ataxia rating scale at trial entry, pre high dose therapy (for patients randomised to Arm C, pre-radiotherapy, post radiotherapy, 2years after trial entry, 5 years after trial entry and at age 18) will be the measures for neurological function.
7. Biological tumour markers. Results of protein expression (including immunohistochemistry), ribonucleic acid (RNA) expression, and DNA analysis assays undertaken on tumour, blood or CSF material collected at diagnosis will be the measures for biological properties.

Completion date
31/12/2032

Eligibility

Key inclusion criteria

Inclusion criteria for trial entry and randomisation 1:
1. 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) subgroup or non-SHH/non-wingless-type (WNT) (Groups 3 and 4) medulloblastoma, with at least one of the following high risk features:
1.1 Metastatic disease: Chang Stage M1, M2 and M3.
1.2 Large cell/Anaplastic MB (as defined by World Health Organisation (WHO) criteria 2016
1.3 Patients with significant residual tumour (> 1.5 cm2) following surgical resection of the primary tumour and other biological risk factors
1.4 Patients with MYC or MYCN amplified tumours (unless MYCN amplified Group 4 without any other high risk factors)
1.5 Patients with SHH subgroup tumours harbouring somatic TP53 mutations.
2. Age at diagnosis > = 3 years. The date of diagnosis is the date on which initial surgery is undertaken.
3. Submission of biological material, including fresh frozen tumour samples and blood, in accordance with national and international schemes for molecular assessment of biological markers, and for associated biological studies.
4. 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
5. Adequate hepatic function defined as:
5.1 Total bilirubin < = 1.5 times upper limit of normal (ULN) for age, unless the patient is known to have Gilbert's syndrome
5.2 ALT or AST < 2.5 X ULN for age
6. Adequate renal function defined as creatinine < 1.5 x ULN
7. Adequate haematological function defined as ANC > = 1 x 109/L; platelets > = 100 x 109/L
8. No significant hearing deficit in at least one ear (significant hearing deficit defined as Chang grade 3 or above)
9. Medically fit to receive protocol treatment
10. Documented negative pregnancy test for female patients of childbearing potential
11. Patient agrees to use effective contraception whilst on treatment (patients of childbearing potential)
12. Written informed consent from the patient and/or parent/legal guardian

Inclusion criteria for Randomisation 2 (R2)
13. Patient entered into the SIOP-HRMB trial at diagnosis
14. Patient treated with either Arm A (conventional radiotherapy) or Arm B (HART) as part of R1

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Key exclusion criteria

Exclusion criteria for trial entry and randomisation 1:
1. Proven or high likelihood of Germline TP53, APC, PTCH, SUFU, PALB2, BRCA2 gene alteration or any other DNA repair defect.
2. Group 4 patients with MYCN amplification and no other high-risk factor
3. β-catenin mutation positive WNT medulloblastoma irrespective of other risk factors
4. Significant residual tumour (> 1.5 cm2) following surgical resection of the primary tumour and no other biological risk factors.
5. Chang Stage M4 disease
6. Brainstem or embryonal tumours in other sites
7. Previously treated for a brain tumour or any type of malignant disease
8. Medical contraindication to radiotherapy or chemotherapy
9. Hypersensitivity to any of the treatments or excipients
10. Females who are pregnant or breastfeeding
11. Cannot be regularly followed up due to psychological, social, family, geographical or other issues
12. Patients for whom non-compliance with treatment, management guidelines or monitoring is expected.

Date of first enrolment
19/01/2021

Date of final enrolment
15/10/2027

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Great North Children's Hospital (lead site)
Royal Victoria Infirmary
Queen Victoria Road
Newcastle Upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
Birmingham

United Kingdom
B4 6NH

Study participating centre
Bristol Royal Hospital for Children
Paul O'Gorman Building
Upper Maudlin Street
Bristol
United Kingdom
BS2 8BJ

Study participating centre
Addenbrooke's Hospital
Hills Road
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United Kingdom
CB2 0QQ

Study participating centre
Alder Hey Children's Hospital
Eaton Road
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L12 2AP

Study participating centre
Christie Hospital
Wilmslow Road
Manchester
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M20 4BX

Study participating centre
Great Ormond Street Hospital for Children
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WC1N 3JH

Study participating centre
John Radcliffe Hospital
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
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Study participating centre
Noah's Ark Children's Hospital for Wales
Heath Park
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United Kingdom
CF14 4XW

Study participating centre
Queen's Medical Centre Nottingham
Derby Road
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NG7 2UH

Study participating centre
Royal Hospital for Children Glasgow
1345 Govan Road
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Study participating centre
Royal Hospital for Sick Children Edinburgh
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EH19 1LK

Study participating centre
Royal Manchester Children's Hospital
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M13 9WL

Study participating centre
Sheffield Children's Hospital
Western Bank
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S10 2TH

Study participating centre
Southampton General Hospital
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Study participating centre
University College London Hospital
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Study participating centre
Clatterbridge Hospital (non-recruiting site)
Clatterbridge Road
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CH63 4JY

Study participating centre
The Queen Elizabeth Hospital (non-recruiting site)
Edgbaston

Birmingham
United Kingdom
B15 2TH

Study participating centre
Velindre Hospital (non-recruiting site)
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Study participating centre
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Whitham Road
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Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK; Grant Codes: C19886/A25241

Results and Publications

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes