High-Risk Neuroblastoma Study 2 of SIOP-Europa-Neuroblastoma (SIOPEN)

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This study has been transitioned to CTIS with ID 2024-514917-36-00 check the CTIS register for the current data. PRIMARY OBJECTIVES*Rx-induction: Comparison of the 3 year EFS rate of 2 induction regimens, GPOH and RAPID COJEC, in patients with high-...

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

Summary

ID

NL-OMON52860

Source
ToetsingOnline

Brief title
HR-NBL2

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Neuroblastoma, tumour of the peripheral autonomic symphatetic nervous system

Research involving
Human

Sponsors and support

Primary sponsor: Institute Gustave Roussy
Source(s) of monetary or material Support: Ministerie van OC&W,Europese Unie

Intervention

Keyword: cancer, chidhood, Neuroblastoma, treatment

Outcome measures

Primary outcome

*Randomization-induction: 3-year EFS from date of R-I randomization.

*Randomization-HDC: 3-year EFS from date of R-HDC randomization.

*Randomization-RTx: 3-year EFS from date of RTx randomization.

*Chemoimmunotherapy arm: Metastatic response rate after 4 cycles of TEMIRI/DB.

Secondary outcome

For the whole population of high-risk neuroblastoma:

*3- and 5-year EFS, PFS and OS calculated from diagnosis

For each treatment phase:

*5-year EFS, 3- and 5-year PFS and OS calculated from the date of randomization/arm inclusion

*Cumulative incidence of relapse/progression

*Cumulative incidence of treatment related mortality and of disease related mortality

*Overall response as per the new INRG response criteria [Park JR, JCO 2017] (including primary tumor after induction), skeletal response on MIBG, bone marrow response, local control

*Therapy-related toxicity

For patients in the chemoimmunotherapy arm:

*Metastatic reponse rate after 2 cycles TEMIRI/DB and 3- and 5-year EFS/PFS/OS

from the date of initial diagnosis

Study description

Background summary

High-risk neuroblastoma represents the largest neuroblastoma subgroup. Prognosis of patients with high-risk neuroblastoma (HR-NBL) remains poor despite multimodal treatment including induction chemotherapy, local treatment (surgery and radiotherapy), high-dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR) and maintenance treatment. As a result of this strategy, the current 3-year event-free survival (EFS) is now around 40% from diagnosis and 55% for those patients who complete all the different parts of the treatment. However, a further improvement in patient outcome is warranted.

Induction chemotherapy is one of the mainstay aspects of multimodal treatment of HR-NBL. Over the last four decades different chemotherapy regimens have been evaluated in this setting by academic cooperative groups with increasing intensity and different combinations of conventional chemotherapeutics. In order to develop the most effective induction chemotherapy regimen and improve overall outcome for HR-NBL, it is necessary to evaluate the induction regimens that are used as standard practice in different regions of the world in a randomized trial.

Questions regarding the optimal consolidation regimen, its interaction with the induction chemotherapy and the role of tandem or multiple regimens remain of major interest on an international level. Bu-Mel was the conditioning regimen mainly used in Europe based on results showing a significant advantage of Bu-Mel in HR-NBL. It is now of major importance to study the impact on survival of an intensified HDC. In order to evaluate the role of tandem HDC in the SIOPEN context, in this trial children with HR-NBL will receive either single HDC Bu-Mel or tandem HDC with Thiotepa and Bu-Mel, followed by ASCR.

External beam radiotherapy has a long history of use in neuroblastoma. Within the SIOPEN group, it is standard practice following induction chemotherapy, surgery and HDC. There is a need for clinical trials to produce high-level evidence to optimize its use in order to improve the current unsatisfactory outcomes. In SIOPEN it has been the practice to give 21.6 Gy radiotherapy to all patients as a standard dose regardless of the disease extent and the quality of surgery. Given the poor prognosis of the HR population, investigation of escalation of the local radiotherapy treatment is highly desirable. We want to address the question whether dose escalation beyond 21.6

Gy would translate into better outcomes in terms of survival for patients with residual disease. This randomization (21.6 Gy vs 21.6 Gy to the preoperative tumor bed + 14.4 Gy boost to the residual tumor) will determine whether patients with macroscopic residual disease after HDC/ASCR and surgery do better with a higher radiotherapy dose.

Study objective

This study has been transitioned to CTIS with ID 2024-514917-36-00 check the CTIS register for the current data.

PRIMARY OBJECTIVES
*Rx-induction: Comparison of the 3 year EFS rate of 2 induction regimens, GPOH and RAPID COJEC, in patients with high-risk neuroblastoma.
*Rx-HDC: Comparison of the 3 year EFS rate from randomization of single HDC with Bu-Mel versus tandem HDC with Thiotepa followed by Bu-Mel in patients with high-risk neuroblastoma and sufficient response to induction chemotherapy
*Rx-Radiotherapy: Comparison of the 3 year EFS rate from randomization of 21.6 Gy radiotherapy to the preoperative tumor bed versus 21.6 Gy radiotherapy and a sequential boost of up to 36 Gy to the residual tumour in patients with macroscopic residual disease after HDC and surgery.
*Chemoimmunotherapy arm: Metastatic response rate after 4 courses of irinotecan-temozolomide (TEMIRI) combined with dinutuximab beta (DB) in patients with insufficient metastatic reponse at the end of induction chemotherapy (TEMIRI/DB).

SECONDARY OBJECTIVES (most important):
*To describe the EFS, PFS and overall survival (OS) from diagnosis of the whole cohort.
*To describe the effect of RAPID COJEC and GPOH induction regimens on metastatic disease during and after the end of induction.
*To assess the correlation of the response of metastatic disease during and after induction with survival (EFS, PFS and OS).
*To describe the effect of HDC with Bu-Mel versus Thiotepa + Bu-Mel on progression-free survival (PFS) and OS.
*To describe and compare the toxicity associated with RAPID COJEC and GPOH induction therapy.
*To describe and compare the acute and long term toxicities of both HDC arms.
*To describe the long term toxicities of dinutuximab beta.
*To investigate the relationship between the quality of surgical resection of the primary tumor, local control and survival.
*To investigate the impact of the radiotherapy dose on local relapse rate.
*To collect data on selected circulating biomarkers, biological and genomic features to determine and compare the effect of these on response to treatment, EFS and OS.
*To describe the 3 and 5-year EFS and OS of patients treated in the chemoimmunotherapy arm with TEMIRI/DB, Thio and Bu-Mel and current high-risk

neuroblastoma local/maintenance treatment
*To describe the metastatic response rate after 2 courses of TEMIRI/DB for patients with insufficient metastatic response at the end of induction chemotherapy
*To describe acute toxicities of the combination of TEMIRI/DB

Study design

This is an international open-label, randomized, multicenter phase III trial including three sequential randomizations to assess efficacy of induction and consolidation chemotherapies, as well as radiotherapy, for patients with high-risk neuroblastoma.

Intervention

Patients will receive:
*INDUCTION CHEMOTHERAPY:
Randomization between RAPID COJEC and GPOH chemotherapy
*SURGERY OF THE PRIMARY TUMOR (according to standard surgical practice in The NL)
* IN CASE OF INSUFFICIENT METASTATIC RESPONSE:
- 4 coursesTEMIRI/DB
*CONSOLIDATION CHEMOTHERAPY
Randomization between single HDC Bu-Mel and tandem HDC consisting in Thiotepa and Bu-Mel, followed by autologous stem cell rescue.
*EXTERNAL RADIOTHERAPIE OF THE PRIMARY TUMOR
-macroscopic residual tumor: Randomization of the dose of radiotherapy; 21,6 Gy. versus 21,6 Gy. + 14,4 Gy. boost.
-no macroscopic residual tumor: 21,6 Gy to the pre-operative tumor bed.
*MAINTENANCE TREATMENT WITH IMMUNOTHERAPY AND ISOTRETINOIN (according to standard surgical practice in The NL)

Study burden and risks

Rx-Induction:
Standard treatment in the Netherlands is GPOH induction. Side effects are known and comparable for both induction schedules. There are no known additional risks. For Dutch patients randomisation for the experimental arm RAPID-COJEC will reduce the duration of induction and days hospitalization (burden).

Rx-HDC:
Standard treatment in the Netherlands is consolidation with HD-BuMel (without HD-Thiotepa). Patients treated with HD-Thiotepa will be in the hospital for about 10 days for administration of medication and recovery. They will be at risk for the adverse events associated with this treatment. These side effects are known and acceptable, because this may contribute to a greater chance of

curation in this population/disease with a poor outcome.

Rx-Radiotherapy:
Standard treatment in the Netherlands is treatment without a boost. Patients treated with boost treatment may have a slightly higher chance of side effects and late effects. Due to the boost, the irradiation may take a few days longer. Local boost could contribute to a better local control and result.

Intensification chemo-immunotherapy:
The standard treatment in the Netherlands is 3x TEM-IRI. In the protocol, Dinutuximab beta is administered in parallel to TEM-IRI for this group with poor prognosis. This combination has shown promising results in relapsed and refractory patients after primary treatment. The additional toxicity of Dinutuximab is limited; most of the observed toxicity is caused by the (standard) TEM-IRI chemotherapy.

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

R-I eligibility criteria:
-Established diagnosis of High-Risk neuroblastoma
-No previous chemotherapyor up to 21days after one cycle of chemotherapy for patients with localized neuroblastoma with MYCN amplification or patients with metastatic neuroblastoma treated in emergency
-Females of childbearing potential must have a negative serum or urine pregnancy test prior to initiation of treatment. Sexually active patients must agree to use acceptable and appropriate contraception while on study drug and for one year after stopping the study drug. Female patients who are lactating must agree to stop breast-feeding.
-Written informed consent to enter the R-I randomization from patient or parents/legal representative, patient, and age-appropriate assent.

R-HDC eligibility criteria:
-High Risk neuroblastoma, EXCEPT patients with stage M 12-18 months old with numerical chromosomal alterations only, and in complete metastatic response at the end of induction.
-Age < 21 years.
-Complete response (CR) or partial response (PR) at metastatic sites:
*Bone disease: MIBG uptake (or FDG-PET uptake for MIBG-nonavid tumors) completely resolved or SIOPEN score <= 3 and at least 50% reduction in mIBG score (or <= 3 bone lesions and at least 50% reduction in number of FDG-PET-avid bone lesions for MIBG-nonavid tumors).
*Bone marrow disease: CR and/or minimal disease (MD) according to International Neuroblastoma Response Criteria [Park JR, JCO 2017; Burchill S, Cancer 2017].
*Other metastatic sites: complete response after induction chemotherapy +/- surgery.
-Acceptable organ function and performance status.
*Performance status >= 50%
*Hematological status: ANC >0.5 x10^9/L, platelets > 20 x10^9/L
*Cardiac function (< grade 2)
*Normal chest X-ray and oxygen saturation
*Absence of any toxicity >= grade 3
-Sufficient collected stem cells available; minimum required: 6 x10^6 CD34+ cells/kg body weight stored in 3 separate fractions
-Written informed consent, including agreement of patient or parents/legal

guardian for minors, to enter the R-HDC randomization.

R-RTx eligibility criteria:
-No evidence of disease progression after HDC/ASCR
-Interval between the last ASCR and radiotherapy start between 60 and 90 days
-Performance status greater or equal 50%
-Hematological status: ANC >0.5 x10^9/L, platelets > 20 x10^9/L
-Written informed consent, including agreement of patient or parents/legal guardian for minors, to enter the R-RTx randomization.

Exclusion criteria

Non-inclusion criteria specific to the R-I randomization (RAPID COJEC/GPOH):
-Urinary tract obstruction >= grade 3
-Heart failure or myocarditis >= grade 2, any arrhythmia or myocardial infection
-Peripheral motor or sensory neuropathy >= grade 3
-Demyelinating form of Charcot-Marie-Tooth syndrome
-Hearing impairment => grade 2
-Concurrent prophylactic use of phenytoin
-Cardiorespiratory disease that contraindicates hyperhydration

Non-inclusion criteria common to all randomizations (R-I, R-HDC and R-RTx) :
-Any negative answer concerning the inclusion criteria of R-I or R-HDC or R-RTx will render the patient ineligible for the corresponding therapy phase randomization. However, these patients may remain on study and be considered to receive standard treatment of the respective therapy phase, and may be potentially eligible for subsequent randomizations.
-Liver function: Alanine aminotransferase (ALT) > 3.0 x ULN and blood bilirubin > 1.5 x ULN (toxicity >= grade 2). In case of toxicity >= grade 2, call national principal investigator study coordinator to discuss the feasibility.
-Renal function: Creatinine clearance and/or GFR < 60 ml/min/1.73m² (toxicity >= grade 2). If GFR < 60ml/min/1.73m², call national principal investigator to discuss about the treatment.
-Dyspnea at rest and/or pulse oximetry <95% in air.
-Any uncontrolled intercurrent illness or infection that in the investigator opinion would impair study participation.
-Patient under guardianship or deprived of his liberty by a judicial or administrative decision or incapable of giving his consent.
-Participating in another clinical study with an IMP while on study treatment.
-Concomittant use with yellow fever vaccine and with live virus or bacterial vaccines.
-Patient allergic to peanut or soya.
-Chronic inflammatory bowel disease and/or bowel obstruction.
-Pregnant or breastfeeding women.
-Known hypersensitivity to the active substance or to any of the excipients of

study drugs known
-Concomitant use with St John*s Wort (Hypericum Perforatum).

Non-inclusion criteria to R-HDC:
Patients with insufficient metastatic response at the end of induction SIOPEN score > 3 or less than 50% reduction in mIBG score or > 3 bone lesions or less 50% reduction in number of FDG-PET-avid bone lesions for mIBG-non avid tumours, will not be elegible for R-HDC

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-03-2021
Enrollment:	70
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:	Cyclophosphamide
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Dacarbazine
Generic name:	Dacarbazine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-10-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-11-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2024

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-08-2024
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	CTIS2024-514917-36-00
EudraCT	EUCTR2019-001068-31-NL
ClinicalTrials.gov	NCT04221035
CCMO	NL72098.041.20