An international multicenter phase II randomised trial evaluating and comparing two intensification treatment strategies for metastatic neuroblastoma patients with a poor response to induction chemotherapy

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Main objective:The main objective is to evaluate the efficacy of two intensified consolidation strategies in very-high risk neuroblastoma (VHR-NBL) patients in terms of event-free survival from randomisation date. Thisevaluation will follow a...

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

Summary

ID

NL-OMON49491

Source
ToetsingOnline

Brief title
VERITAS

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: Gustave Roussy
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cancer, children, Neuroblastoma, refractory

Outcome measures

Primary outcome

The primary endpoint is the 3 years Event-Free Survival from the date of randomisation into the VERITAS trial, considering as events: disease progression or relapse, death from any cause, and secondary malignancy. Patients without event are censored at the date of their last follow up evaluation.

Secondary outcome

a - Overall survival, defined as the time from randomisation to death from any cause.

b - Adverse events, evaluated using NCI-CTCAE v4.0 toxicity grading system, reported by treatment phase and overall over the whole treatment duration (maximum grade). The stopping rule for toxicity will be based on the occurrence of adverse events leading to ventilation in an ICU and treatment-related deaths. These events will be specifically monitored over the first 6 months after

randomisation.

c - Disease response after BuMel and at the end of treatment

d - For the Q-TWiST analysis: time spent with severe toxicity after

randomisation and before

progression/relapse (duration of hospitalisation will be used as a surrogate of

time with toxicity);

time spent without progression/relapse and without toxicity; and time from

progression until death.

e - Logistical issues raised by 131I-mIBG and topotecan or Thiotepa therapy in

a multicenter setting

f - Event-Free Survival from the date of start of the consolidation phase

g - Event-Free Survival from the date of the neuroblastoma diagnosis

Study description

Background summary

High-risk neuroblastoma remains one of the major challenges in paediatric oncology. Despite the introduction of high-dose chemotherapy with haemopoietic stem cell support, the outcome of these patients remains poor. This is particularly so for patients who respond poorly to initial chemotherapy. If metastatic CR is achieved after induction, patients proceed directly to the consolidation therapy consisting of BuMel and peripheral blood stem cells transplantation (PBSCT).
Patients with primary refractory or poorly responding disease need effective salvage treatment if they are to be cured. At the present time there is no salvage therapy generally recognized as sufficiently effective for this patient group, and the prognosis remains very poor. For these patients with primary refractory or poorly responding disease, there are no current guidelines for treatment. Audits of care have shown a range of different treatment approaches. Separate national or institutional groups have piloted alternative treatment strategies, some of which appear to be promising, and a formal comparison of

these is appropriate.

Study objective

Main objective:
The main objective is to evaluate the efficacy of two intensified consolidation strategies in very-high risk neuroblastoma (VHR-NBL) patients in terms of event-free survival from randomisation date. This
evaluation will follow a hierarchical testing procedure: each experimental treatment will be first evaluated as a single-arm phase 2 study, and in case of positive conclusion, the relative efficacy of both arms will then be evaluated comparatively.

Secondary objectives:
a - To estimate and compare the overall survival (OS) of patients treated in the two treatment
strategies
b - To evaluate and compare the safety of the two treatment strategies in terms of toxic death and
non-fatal toxicities rates.
c - To estimate and compare the disease response after BuMel and at the end of treatment of the two
treatment strategies
d - To evaluate the between-treatment differences in Quality adjusted Time Without Symptoms and
Toxicity (Q-TWIST approach)
e - To evaluate the feasibility and document the logistical issues raised by 131I-mIBG and topotecan
therapy in a multicenter setting
f - To estimate and compare the Event-Free Survival of the two treatment strategies from the start of
the intensified consolidation chemotherapy
g - To estimate and compare the Event-Free Survival of the two treatment strategies from the date of
the neuroblastoma diagnosis

Study design

Prospective, open-label, randomised, multi-centre, phase-II trial

Intervention

The trial will evaluate two randomised arms. Each arm includes three cycles of Temozolomide-Irinotecan (similar in both arms), a specific consolidation course detailed hereinafter, a BuMel sequence, followed by an autologous stem cell transplant (similar in both arms), external radiotherapy as appropriate, and/or

local surgery of the tumour residues as appropriate.

The specific consolidation courses differ between the randomised arms as follows: Two courses 131-I- mIBG and Topotecan with peripheral blood stem cell rescue (ARM A) or High dose thiotepa with peripheral blood stem cell rescue (ARM B).

Study burden and risks

The VERITAS protocol is an intensification of the already very intensive HR-NBL standard protocol, for patients with insufficient response after the induction chemotherapy. The treatment within VERITAS is very intensive. For the high dose chemotherapy + ASCR and MIBG therapy, patients are hospitalized for a long time. Patients are cared in isolation during the MIBG therapy and isolation guidelines are in place. All patients suffer from side effects during treatment and possibly with late effects long after treatment.

Not everything in the VERITAS is an additional burden. Many parts of the treatment are also part of the standard high-risk treatment or the individual treatment plan for patients who need treatment intensification. Intensification of the treatment gives patients a chance to achieve a better result and gives the possibility to continue with the standard protocol maintenance. It gives a possible last chance of long-term disease control, cure and survival.

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)
Elderly (65 years and older)

Inclusion criteria

1. Metastatic neuroblastoma (NBL).
2. Previously treated within the ongoing High Risk Neuroblastoma SIOPEN study.
3. 131I-mIBG scintigraphy positive at diagnosis and after induction chemotherapy (before high-dose BuMel + ASCT).
4. Metastatic response after induction chemotherapy lower to the ongoing High Risk Neuroblastoma
SIOPEN trial criteria to be eligible for High Dose Chemotherapy; metastatic response worse than
partial response (< PR) or SIOPEN score >= 3.
5. Females of childbearing potential must have a negative serum pregnancy test within 7 days 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. Acceptable
contraception are defined in CTFG Guidelines *Recommendations related to contraception and
pregnancy testing in clinical trials*. Female patients who are lacting must agree to stop breastfeeding.
6. Written informed consent from parents/legal representative, patient, and age-appropriate assent
before any study-specific screening procedures are conducted according to local, regional or
national guidelines.
7. Patient affiliated to a social security regimen or beneficiary of the same according to local
requirements.

Exclusion criteria

1. Parenchymal brain metastasis(es) (even one)
2. Progressive disease at study entry
3. Previous high-dose therapy and PBSCT
4. Performance status (Karnofsky or Lansky) <70%
5. Patient having received other therapy for cancer treatment than those allowed as per the ongoing
High Risk Neuroblastoma SIOPEN trial or as defined in the future frontlines protocol (for HRNBL1
trial : after induction + 2 TVD)
6. Impaired organ function (liver, kidney, heart, lungs) according to the following definitions
o Shortening fraction <28%, or ejection fraction <55%, or clinical evidence of congestive heart
failure or uncontrolled cardiac rythm disturbance
o Dyspnea at rest and/or pulse oxymetry <95% in air.
o ALT, Bilirubin >= 2 ULN
o Creatinine clearance and/or GFR <= 60 ml/min/1.73m2 and serum creatinine < 1.5 mg/dl
7. Any uncontrolled intercurrent illness or infection that in the investigator*s opinion would impair
study participation
8. Concomitant use with yellow fever vaccine and with live virus and bacterial vaccines
9. Patient allergic to peanut or soya
10. Chronic inflammatory bowel disease and/or bowel obstruction
11. Pregnant or breastfeeding women
12. Known hypersensitivity to the active substance or to any of the excipients of study drugs
13. Known hypersensitivity to dacarbazine
14. Concomitant use with St John's Wort

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-02-2020
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	131-Iodine meta-iodobenzylguanidine
Generic name:	131-Iodine meta-iodobenzylguanidine
Product type:	Medicine
Brand name:	Busulfan
Generic name:	Busulfan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Temozolomide
Generic name:	Temozolomide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Thiotepa
Generic name:	Thiotepa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Topotecan
Generic name:	Topotecan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-07-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-09-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-04-2021
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
EudraCT	EUCTR2015-003130-27-NL
ClinicalTrials.gov	NCT03165292
CCMO	NL68701.041.19