RANDOMIZED PHASE 2 TRIAL COMPARING EXPERIMENTAL IMMUNOTHERAPY (ANTI-GD2 ANTIBODY, IL-2 S.C.,GM-CSF) IN RECURRENT HIGH RISK NEUROBLASTOMA PATIENTS WITH STANDARD IMMUNOTHERAPY (ANTI-GD2 ANTIBODY, IL-2 I.V., GM-CSF) IN PATIENTS WITH RECURRENT AND NEWLY DIAGNOSED HIGH RISK NEUROBLASTOMA

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Primary end points:Safety (>1 toxic death per arm) and tolerability (relevant grade 4 toxicities) in not more than 33% of patients for the three treatment arms.Secondary end points:* Reduction of grade 2-4 key side effects in the experimental arm...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON44066

Source
ToetsingOnline

Brief title
NB2013-HR PILOT GPOH/DCOG

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
cancer, neuroblastoma

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Kinderoncologie Nederland
Source(s) of monetary or material Support: Leverkusen hilft krebskranken Kindern e.V. Germany,United Therapeutics

Intervention

Keyword: children, high risk, immunotherapy, neuroblastoma

Outcome measures

Primary outcome

Safety (toxic deaths) and tolerability (relevant grade 4 toxicities) for the

three treatment arms.

Secondary outcome

* Reduction of grade 2-4 key side effects in the experimental arm by * 30 %

compared to the standard arm. Key side effects are presence of capillary leak

and cytokine release syndromes. They will be assessed collectively.

* Neuralgia (with assessment of pain duration (days requiring morphin) and

maximum grade of pain scores during first 2 antibody cycles) will be evaluated

descriptive in both arms. No difference between the arms is expected.

* Comparison of pharmacokinetics of antibody ch14.18 (levels of antibody and

presence of antiidiotype antibodies) in both arms (descriptive)

* Comparison of immune response (antiidiotype antibodies, immune cell

phenotypes, immune mediators, functional assays as ADCC and CDC) between treatment cycles, treatment arms and between recurrent and newly diagnosed patients (descriptive).

* Comparison of grade 2-4 toxicities (ascites, ARDS, dyspnoea, hypotension in addition to capillary leak and cytokine release syndromes) between intravenously and subcutaneously administered IL-2 (standard vs. experimental arm and recurrent vs. newly diagnosed patients) (descriptive).

* 2 year event free (EFS), progression free (PFS) and overall survival rates (OS) from time of randomization. 2 year minimum follow-up for at least 24 enrolled patients (descriptive).

* Tumor response at the end of treatment and time to progression (TTP)

* Quality of Life (QoL) evaluated by parents using PedsQL questionnaires with scale rating (descriptive comparison between the standard and the experimental arm).

Study description

Background summary

Although the five year survival rate of children with high risk neuroblastoma have increased over the last three decades from 4 to 44 % (1), neuroblastoma is the second most frequent cause for cancer related death in childhood (11 %). Most patients show good initial response rates (CR + PR rate 95 %), but 55 % experience a largely treatment-resistant tumor progression.
Recently, a breakthrough with immunotherapy was reported by US investigators from the Children*s Oncology Group (2) using the anti-GD2 monoclonal antibody ch14.18 for tumor cell destruction and GM-CSF plus interleukin 2 for immunostimulation. This immunopackage resulted in an increase of 20 % EFS at 2 year from randomization. However, this was associated with a high toxicity rate (pain, capillary leak syndrome).
The proposed trial compares the COG *standard of care* arm (anti-GD2 + GM-CSF +

IL-2 i.v. + retinoic acid oral) with an experimental arm (anti-GD2 + GM-CSF + IL-2 s.c. + retinoic acid oral) designed to reduce toxicity.
The potential benefit from this trial consists of the confirmation that the American trial design is feasible in an independent set of patients with different preceding therapy, at a different time point regarding to immune reconstitution after ASCT, the feasibility of a newly designed immunotherapy (which is hopefully less toxic) and the investigation of immune response parameters. This pilot study is the prerequisite for a consecutive randomized clinical trial comparing two immunotherapeutic approaches in a larger set of patients.

Study objective

Primary end points:
Safety (>1 toxic death per arm) and tolerability (relevant grade 4 toxicities) in not more than 33% of patients for the three treatment arms.

Secondary end points:
* Reduction of grade 2-4 key side effects in the experimental arm by * 30 % compared to the standard arm. Key side effects are presence of capillary leak and cytokine release syndromes. They will be assessed collectively.
* Neuralgia (with assessment of pain duration (days requiring morphin) and maximum grade of pain scores during first 2 antibody cycles) will be evaluated descriptive in both arms. No difference between the arms is expected.
* Comparison of pharmacokinetics of antibody ch14.18 in both arms (levels of antibody and presence of anti idiotype antibodies, descriptive)
* Comparison of immune response (immune cell phenotypes, immune mediators, functional assays as ADCC and CDC) between treatment cycles, treatment arms and between recurrent and newly diagnosed patients (descriptive).
* Comparison of grade 2-4 toxicities (ascites, ARDS, dyspnoea, hypotension) between intravenously and subcutaneously administered IL-2 (standard vs. experimental arm) and recurrent vs. newly diagnosed patients (descriptive).
* 2 year event free (EFS), progression free (PFS), and overall survival rates (OS) from time of randomization. 2 year follow-up for at least 24 enrolled patients (descriptive) The time counts from end of therapy of the last enrolled living patient.
* Tumor response at the end of treatment and time to progression (TTP)
* Quality of Life (QoL) evaluated by parents rating (Descriptive comparison between the standard and the experimental arm).

Study design

The NB2013-HR pilot GPOH/ DCOG trial is a randomized, phase 2, open label, prospective, multicenter, multinational clinical trial comparing COG immunotherapy as the currently best available treatment (standard arm) with a new anti GD2-based immunotherapy (experimental arm).

This is a randomized, open label, prospective, multicenter, multinational clinical trial.
Bias is minimized by randomized group allocation stratified by the established risk factors
* Stage (1/2/3/4S vs. 4)
* *MYCN amplification* (yes vs. no) and
* Remission status at trial entry (CR/VGPR vs. PR/SD)

Thus, the following strata exist:
Table 2: Stratification of randomisation:
Expected percentage of patients Stratum no INSS stage MYCN amplification Remission status at trial entry
10% 1 1/2/3/4S yes CR/VGPR
2 1/2/3/4S yes PR/SD
90% 3 4 Yes CR/VGPR
4 4 Yes PR/SD
5 4 No CR/VGPR
6 4 No PR/SD

Previous trials demonstrated a high randomization compliance rate (NB2004-HR >95%), thus a very good acceptance rate of this trial and a representative trial population can be assumed. A blinding procedure will not be feasible due to the different medications, the different time schedule and the different side effect spectrum.

Intervention

The intervention is scheduled
* in patients with recurrent or progressive neuroblastoma after re-induction chemotherapy and at least disease stabilisation.
* in patients with de novo neuroblastoma after myeloablative treatment with autologous stem cell reinfusion and at least disease stabilisation

Study burden and risks

not applicable

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Established diagnosis of neuroblastoma according to the international INSS criteria;High risk (HR): stage 4 over 18 months of age and MYCN amplified neuroblastoma of any stage and any age
- Recurrent or progressive neuroblastoma: completed re-induction chemotherapy (Germany and The Netherlands)
- Newly diagnosed neuroblastoma: Complete front-line treatment including induction chemotherapy, surgical removal and/ or local irradiation of the primary tumor and myeloablative chemotherapy with autologous stem cell reinfusion according to the actual guidelines of the GPOH/ DCOG (in The Netherlands only).;Achieved response status: stable disease or better (CR, VGPR, PR, SD) at the end of re-induction chemotherapy in recurrent disease and after ASCT in newly diagnosed disease;Written informed consent of parents or guardian and * if appropriate * of the patient.;For at least two weeks prior to start of trial medication
- off any standard or experimental treatment (and fully recovered from short-term major toxic effects)
- no tumour surgery (and fully recovered from any post-surgical complications)
- no immediate requirements for palliative chemotherapy, radiotherapy or surgery;The patient may have had prior CNS metastases provided the following criteria are all met:
- The patient*s CNS disease has been previously treated

- The patient*s CNS disease has been clinically stable for four weeks prior to starting this study (assessed clinically and by MRI or CT)
- The patient is off steroids for four weeks prior to starting the study and will not require them during the course of the study
- A patient with seizure disorders may be enrolled if well controlled on anticonvulsants and if no seizures have occurred within a 6 week period prior to starting trial treatment ;HIV sero-negative and neither active nor chronic-replicative hepatitis B infection ;adequate functions of the cor, lung, bone marrow, liver, kidney

Exclusion criteria

Significant intercurrent illnesses and/or any of the following:
- Symptoms of congestive heart failure or of uncontrolled cardiac arrhythmia
- Significant psychiatric disabilities or psychological conditions preventing treatment realization
- Uncontrolled seizure disorders
- Active infections
- Clinically significant neurologic deficit or objective peripheral neuropathy (> grade 2)
- Significant, symptomatic pleural effusions;Requirement or likely requirement for corticosteroids or other immunosuppressive drugs (except the medications recommended for conditions mentioned in the protocol);Platelet transfusion dependency;Concurrent treatment with any non-trial anticancer therapy or interventional study;Positive pregnancy test, lactation;Sexually active patients (male and female) at reproductive age not willing to use highly effective contraceptive methods according to the guidelines ICH M3 ;Neuroblastoma patients with actively progressing disease;Patients with HACA detected after previous antiGD2 immunotherapy;Known allergy or contraindications against one of the study drugs (IMP)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Aldesleukin, e.g. Proleukin S
Generic name:	IL-2
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	dinutuximab : Unituxin
Generic name:	chimeric monoconall antibody 14.18
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Isotretinoin-ratiopharm
Generic name:	Roaccutane
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sagramostim, Leukine
Generic name:	GM-CSF

Ethics review

Approved WMO

Date:	24-02-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	06-10-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2013-004481-34-NL
CCMO	NL55580.078.15