Phase II trial of the combination of gemcitabine and 131I-MIBG therapy in paediatric patients with relapsed or progressive neuroblastoma

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To evaluate the efficacy and toxicity of gemcitabine in combination wth 131I-MIBG in pediatric patients with relapsed or progressive neuroblastoma.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON39557

Source
ToetsingOnline

Brief title
MIBG-Gem

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
neuroblastoma in children

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,collectebusfondsen

Intervention

Keyword: 131I-MIBG, children, gemcitabine, neuroblastoma

Outcome measures

Primary outcome

To assess the objective response rate of the combination of gemcitabine and

131I-MIBG (MIBG-gem) in children with relapsed or progressive neuroblastoma.

Response rate will be assessed per stratum: MIBG pretreated and MIBG-naieve.

The duration of response, time to progression and survival will be assessed.

To characterise safety and toxicity profile of this combination treatment.

Secondary outcome

none

Study description

Background summary

Pediatric tumors are rare and neuroblastoma accounts for 10% of all childhood cancers. Neuroblastoma can present in different stages, stage IV in patients older than 1 year of age represents the most frequent form. This stage is diagnosed in the Netherlands in 25 patients per year. The overall cure rate for childhood cancer with current treatment protocols is approximately 70%, buit cancer is still the leading cause of death due to disease in children. Despite intensive treatment for neuroblastoma stage IV disease cure rate is far worse: a 5-year survival rate of only 30-40%. Therefore, we urgently need new drug to improve prognosis.

In this study we aim at assessing the efficacy and toxicity of the combination of gemcitabine and 131I-MIBG in children with relapsed or progressive neuroblastoma. Children will be divided in 2 strata: MIBG pretreated and MIBG-naive.
Gemcitabine is a type of drug (anti-metabolite) which is currently not available in the treatment protocols. Its activity is extensively shown in solid tumours in adults. Furthermore, since gemcitabine has a radiosensitizing effect, it is part of the combination treatment with external beam radiotherapy

in the treatment of some adult tumours. Extensively preclinical evidence has proven that gemcitabine as a single drug is quite effective in neuroblastoma cell lines. In phase I studies with gemcitabine in children, a mild toxicity profile was seen. The maximum tolerated dose (MTD) of gemcitabine single agent in children with solid tumors is 1200 mg/m2/dose (3 weeks, 1 weeks rest). The dosages at which gemcitabine shows radiosensitizing effect are much lower than the MTD. In this study, we will use a startdose of gemcitabine of 375 mg/m2/ dose. See further design.
131I-MIBG single agent has shown its efficacy in patients with neuroblastoma both in upfront and in relapse setting with response rates in relapse setting of 10-43%. Given the radiosensitising effect and the mild toxicity profile we feel the combination of gemcitabine and 131I-MIBG warrants further clinical investigation.

Study objective

To evaluate the efficacy and toxicity of gemcitabine in combination wth 131I-MIBG in pediatric patients with relapsed or progressive neuroblastoma.

Study design

This multi-center study will be performed in collaboration with German Pediatric Oncology Hematology Group (GPOH) in 10-12 different centres in the Netherlands, Germany and Hong-Kong. It is a single-arm study according to a 2-stage design with stopping rules for efficacy and toxicity. We start with a dose of 375 mg/m2/dose of gemcitabine. When 6 patients have been treated at the first dose-level a safety analysis will be performed. If dose-limiting toxicity is encountered in 2 or more patients, the trial stops or will be amended (dosing, interval). Otherwise, enrolment will be continued until 19 patients have been treated. Then an interim analysis will be performed after which, in case of intermediate reponse and no severe toxicity, study will be continued with an escalated dose (500 mg/m2). If response rates are very high at interim analysis and there's limited toxicity, enrollment will be continued at the same dose of gemcitabine (375 mg/m2) up to 47 patients. If study is continued at the escalated dose level, another safety analysis will be performed after treating the first 6 patients and an interim analysis will be perfomed after 19 patients at that dose.
Patient numbers will be balanced per stratum based on previous MIBG-treatment, enrollment will be continued until a minimum of patients are included per stratum.
(see the protocol for statistical details)

Intervention

Treatment consists of gemcitabine 375 mg/m2 IV in 30 minutes, followed by

131I-MIBG 444 Mbq/kg IV over 1 hour on day 1 in a cycle of 28 days. On Day 8 gemcitabine 375 mg/m2 IV in 30 minutes is given.
Following the treatment with 131I-MIBG the child will be admitted and isolated to a nuclear medicine ward for 3-5 days at the beginning of the cycle. Children may be released from the nuclear medicine ward if exposure rate is below a treshold. On Day 8 gemcitabine infusion will be given at the day-care unit after which the child can go home.
After 1 cycles response will be assessed. If the patient has clinical benefit and toxicity is mild, combination treatment can be continued until a maximum of 6 cycles.

Study burden and risks

Treatment consists of 1-2 x 3-5 days admission to a nuclear medicine ward and 2-4x administration of chemotherapy at the day-care unit. Additional visits to the hospital may be needed for tumor evalution.

At inclusion we will perform physical examination, tumor evaluation (scans), blood tests and urine sampling.
During treatment blood tests will be done and chemotherapy is given
Follow-up: tumor evaluation and blood tests will be done.

Common risks during chemotherapy: nausea and vomiting, leukocytopenia and thrombocyotpenia

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

- relapsed or progressive neuroblastoma
- age 1 up to 18 years
- measurable or evaluable disease
- evidence of sufficient MIBG uptake in bone or soft tissue
-lansky play score > 70 or ECOG 1
- adequate organ function
- life expectancy > 6 weeks
- wash out of prior therapy of 3 weeks; (1 week if vincristine, 6 weeks in case of nitrosureas); 6 months in case of ASCT
- written informed consent

Exclusion criteria

-other anti-tumour therapy
- symptomatic brain metastasis
- contra-indication for nuclear isolation
- hypersensitivity to gemcitabine

Study design

Design

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

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-03-2011
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	131I-Metaiodobenzylguanidine
Generic name:	131I-Metaiodobenzylguanidine
Product type:	Medicine
Brand name:	gemcitabine
Generic name:	gemcitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	02-07-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	12-06-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2007-007974-45-NL
CCMO	NL20757.018.08