Middle ear thiosulfate-gel protection against cisplatin-induced hearing loss in patients carrying a single nucleotide polymorphism in the TPMT, COMT or LRP2 gene

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The primary objective of this study is to proof the concept that cisplatin-induced ototoxicity can be prevented by transtympanic STS containing gel application, through inserted grommets.The STS containing and blank gel formulations will be provided...

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

Summary

ID

NL-OMON47112

Source
ToetsingOnline

Brief title
N12MTG

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
ototoxicity ; hearing loss

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Nederlands Kanker Instituut - Antoni van Leeuwenhoek ziekenhuis

Intervention

Keyword: cisplatin, ototoxicity, sodiumthiosulphate

Outcome measures

Primary outcome

Audiometric tests after each cycle will be compared to baseline audiometric

tests to measure the development of the occurence of ototoxicity and 4 weeks en

3 months after the last cycle of cisplatin.

Secondary outcome

To determine the feasibility and safety of repeated application of a STS

containing or placebo gel formulation to the middle ear through a grommet (arm

A)

To determine the feasibility and safety of repeated application of STS

containing gel formulation by direct puncture of the ear drum (arm B).

To determine the pharmacokinetics of platinum in plasma (bound and unbound) in

these patients.

On exploratory basis patients will be screened for genetic variants in the

TPMT, COMT, LRP2, GSTP1, GSTM1 and OCT2. Previous prospective studies performed

and prescirbed in literature have shown a possible relation of genetic

variations in these genes to the development of ototoxicity in patients treated

with cisplatin.

Study description

Background summary

Platinum drugs are effective chemotherapeutic agents widely used for the treatment of various types of adult and pediatric cancers. Clinical application of cisplatin however causes severe and irreversible toxicity including neurotoxicity, nephrotoxicity and ototoxicity. Nephrotoxicity is limited with forced diuresis pre- and post-infusion. Ototoxicity however can not be cured and is permanent in the majority of patients treated with cisplatinum. It affects the inner ear which is essential in both hearing and balance. Platinum-induced toxicity is caused by high doses of administered cisplatin intravenously or intraperitoneally. Cisplatin induces dose-dependant death of cochlear cells, mostly outer hair cells (OHC*s). It targets DNA of proliferating cells to achieve anti-tumor activity. Cisplatin is activated by the replacement of one of its two chloride groups by a water molecule. Activated mono-aqua cisplatin binds to DNA which forms intra- and interstrand complexes that lead to inhibition of DNA synthesis, suppression of RNA transcription, cell cycle arrest and ultimately apoptosis.

Study objective

The primary objective of this study is to proof the concept that cisplatin-induced ototoxicity can be prevented by transtympanic STS containing gel application, through inserted grommets.

The STS containing and blank gel formulations will be provided by the pharmacy department of the Slotervaart Hospital. Patients with advanced cancer treated with cisplatin according to standard of care will be consented for this clinical proof of concept study. In total six evaluable patients will be included. The investigational medicinal products consist of a 0.1M STS in a 0.5% w/w HYA in PBS gel formulation and the blank gel, consisting of the same formulation without STS. A volume of 1.0 ml of the STS containing and blank gel will be injected into the middle ear of the consented patients. Patients will be treated with cisplatin at a minimal dose of 75 mg/m2 or more, for a minimum of three cycles (q=3weeks), if in the best interest of the patient. The transtympanic injection will take place three hours prior to the start of each cycle of cisplatin treatment. Patients will be randomized whereby right and left ear will be injected with the STS containing gel or blank gel. Every next cycle the STS containing gel and blank gel, respectively, will be administered to the same ear as during the first cycle.

Study design

A pharmaceutical, pharmacological, otological, audiological, randomized

clinical phase 1 study

Intervention

Arm A
In order to prevent the development of ototoxicity STS containing transtympanic injections will be applied three hours prior to each first administration of cisplatin treatment in each cycle. Through randomization it will be decided in which ear patients will receive the STS containing gel or blank gel.

Arm B
By randomization it will be decided which ear will be treated with natriumthiosulfate in this ear a grommet will be placed. Via direct puncture of the ear drum the natriumthiosulfate will be injected (in arm A this was done via the grommet). The non randomized ear will remain untreated.

Study burden and risks

After written informed consent, grommets will be inserted prior to start of the study after which the transtympanic injections will be performed.

Physical examiniation, laboratory assessments, audiometric tests will be performed prior to start of each cycle. Patients will visit the hospital weekly for physical examination. On cycle 1 day 1 patients will be hospitalized for one day on wich pharmacokinetic sampling will be performed. In total 8 blood samples will be taken on different time point during the day. Also after 2 cycles a CT scan will be performed. Genetic sampling will take place during the pharmacokinetic sampling.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histological or cytological proof of advanced cancer for which cisplatin treatment at a minimal dose of 75 mg/m2 per 21 days is considered of benefit; for example non-small cell lung cancer; patients with a head and neck malignancy of the oropharynx, hypofarynx, oral cavity and larynx with blue or brown eyes.
2. Age * 18 years;
3. Able and willing to give written informed consent;
4. WHO performance status of 0, 1 or 2;
5. No relevant otological history; (presbyacusis, conductive hearing loss, air-bone gap (ABG), complaints of tinnitus or vertigo, ototoxic co-medication (see appendix VI), chronic middle ear infections, trauma, operations, or hearing aid) ,
6. Able and willing to undergo blood sampling for PK analysis and genetic analysis for specific SNPs;
7. Minimal acceptable safety laboratory values;
a. ANC of * 1.5 x 109 /L
b. Platelet count of * 100 x 109 /L
c. Hepatic function as defined by serum bilirubin * 1.5 x ULN, ALAT and ASAT * 2.5 x ULN or *5 x ULN in case of liver metastases
d. Renal function as defined by serum creatinine * 2.5 x ULN or creatinine clearance * 60 ml/min (by Cockcroft-Gault formula).
8. Negative pregnancy test (urine/serum) for female patients with childbearing potential;
9. Combined treatment of cisplatin with other cytostatic, cytotoxic or radiation therapy according to local treatment guidelines is permitted. However, radiation therapy to the head and neck region is excluded.

Exclusion criteria

1. Any treatment with investigational drugs or other antineoplastic therapy within 21 days

prior to receiving the first dose of investigational treatment;
2. Patients who have had previous systemic treatment with cisplatin or oxaliplatin; (HIPEC and other local non systemic therapy are allowed)
3. Known hypersensitivity to STS containing HYA gel formulation;
4. Patients with symptomatic brain metastases, carcinomatous leptomeningitis at start;
5. Woman who are pregnant or breast feeding;
6. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients;
7. Patients with a known history of hepatitis B or C;
8. Patients with a head and neck malignancy other than; oropharynx, hypopharynx, oral cavity and larynx or patients with a head and neck malignancy green eyes.
9. Any condition that would, in the investigator judgement contraindicate the patients participation in the clinical study due to safety concerns or compliance with clinical study procedures

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-06-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Sodiumthiosulphate

Ethics review

Approved WMO Date:	09-01-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-02-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-02-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	06-04-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-04-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2012-004653-80-NL
CCMO	NL42566.031.12