A randomized double-blind study of N-Acetylcysteine vs. placebo to Prevent Neurotoxicity induced by Platinum containing chemotherapy in patients treated for (Non)Small Cell Lung Cancer and Malignant Mesothelioma.

Published: 12-10-2007
Last updated: 10-05-2024

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Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON31618

Source
ToetsingOnline

Brief title
NAC-PNP-study

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Peripheral neuropathies
- Respiratory tract neoplasms

Synonym
hypo-esthesia, numbness

Research involving
Human

Sponsors and support

Primary sponsor: Rijnstate Ziekenhuis
Source(s) of monetary or material Support: Afdeling Longziekten;Rijnstate

Intervention

Keyword: cisplatin, glutathione, NAC, neuropathy

Outcome measures

Primary outcome

The main study parameter is the occurrence of peripheral neuropathy: therefore the NAC-arm and the placebo-arm will be compared regarding the peripheral neuropathy score (PNP-score) and the electrophysiological measurements.

Secondary outcome

Secondary parameters are the occurrence of differences in haematological pathology, creatinine clearance, liver chemistry and KPS, between the NAC-arm compared to the placebo-arm. Quality of Life will be assessed according to the EORTC QLQ-questionnaire. Differences in tumour response between the two groups will be compared.

Study description

Background summary

Cisplatin (CDDP) and carboplatin are major compounds of chemotherapy in patients with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and malignant mesothelioma. Cisplatin is associated with a number of side-effects, one of which is neurotoxicity. For a number of patients this neurotoxicity is a dose-limiting side-effect. At this point no measures are taken to prevent the occurrence of this neurotoxicity during treatment with

cisplatin. Recent studies have shown that the association of anti-oxidants to treatment with cisplatin has a neuroprotective effect without loss of anti-tumour efficacy of cisplatin. One of these anti-oxidants is glutathione (GSH), this is a natural anti-oxidant that is synthesized in all cells, mainly in the liver and the muscles. This GSH plays a central role in the pathophysiology of cisplatin. We want to investigate the efficacy of N-acetylcysteine (NAC), which serves as a substrate for the synthesis of GSH, in the prevention of cisplatin-induced neurotoxicity. NAC has been shown to increase the GSH levels in the serum, it is also according to this principle that NAC is currently used in the treatment of acetaminophen-(paracetamol)-intoxications, where it replenishes the GSH-depletion of the liver.

Study objective

The primary objective is to establish the neuroprotective efficacy of NAC against cisplatin-induced neurotoxicity. Mainly the sensory neuronal guidance will be assessed before and after treatment with cisplatin in a group of patients receiving NAC compared to a control-group receiving placebo. The secondary objectives are establishing the protective effect of NAC regarding other cisplatin-induced side-effects such as haematological pathology (anaemia, leucopenia, thrombopenia, febrile neutropenia), loss of creatinine clearance and occurrence of liver-chemistry abnormalities. Secondary objectives include also establishing the effect on tumour response, clinical performance (Karnofski performance index) and quality of life.

Study design

Monocenter, non-academical teaching hospital, double-blind randomized placebo-controlled study.

Intervention

Patients will be randomized in a placebo-arm and a NAC-arm. They will receive intravenous study-medication every 3 weeks, each time 6 hours after the completion of the cisplatin-infusion.

Study burden and risks

Burdens: The most important burden is the electromyographic (EMG) testing, which will normally take place 3 times during the course of the whole treatment, therefore patients will have to visit the hospital to be measured. To minimize this burden, the EMG-measurements will be planned on the same day, the patient has to visit the hospital for reasons regarding his/her regular chemotherapy-treatment. Only surface patch electrodes will be used (no needle electrodes). All other information will be obtained from the patients* files

(blood samples, physic evaluations, etc) these are considered to be part of the routines of treatment. Patients will have to fill in Quality of Life questionnaires.
Risks: For intravenous NAC, allergic reactions have been reported. There is also a theoretical risk, that NAC may reduce anti-tumour efficacy of cisplatin, this risk will be theoretically ruled out by appropiate dosing of NAC. After inclusion of the first 30 patients an interim analysis will be performed regarding the tumour response.
Benefits: NAC will possibly prevent the occurrence of neurotoxicity, improving quality of life. This may, in turn, result in less probability of dose-reductions and of pre-term arrest of treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-diagnose is histologically or cytologically proven (NSCLC,SCLC), malignant mesothelioma (histologically)
-at least 4 cycles of cisplatin are planned
-adequate renal function (creatinine clearance as calculated by Cockroft-Gault method > 60 ml/min)
- Karnofski performance score > 60 %
-written informed consent
-patient must be able to comply with study measurements i.e. hospital visits for EMG and QoL assessments
-age >= 18 years

Exclusion criteria

-patients with pre-existing neuropathy
-patients not willing to stop earlier prescribed NAC
-patients not willing to stop vitamins E and A above daily advisory dosage
-uncontrolled metastasis in the central or peripheral nervous system

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N-acetylcysteine
Generic name:	N-acetylcysteine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-10-2007
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2008
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2007-002787-95-NL
Other	in behandeling bij NTR
CCMO	NL19614.091.07