Pilot study: Is concomitant administration of lidocaine during oxaliplatin infusion able to prevent pain as a result of oxaliplatin induced acute neuropathy?

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Primary objectiveTo evaluate the efficacy of low dose intravenously lidocaine in comparison with placebo in terms of pain relief after the first oxaliplatin administration measured by a numeric rating scale (NRS 0-10).Secondary objectives1....

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON42676

Source
ToetsingOnline

Brief title
LiON

Condition

- Other condition
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Oxaliplatin induced nerve pain

Health condition

Pijngeneeskunde

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Gastro-intestinal tumors, Lidocaine, oxaliplatin, polyneuropathie

Outcome measures

Primary outcome

Difference in NRS before and after the first oxaliplatin infusion

Secondary outcome

Difference in NRS before and after the following oxaliplatin infusions (cycle

2-8, 3 month follow up)

Cytokine en ICAM-1 levels before and after the first oxaliplatin infusion

Results obtained from the following questionnaires

- NCI-CTC at baseline, before each oxaliplatin infusion and at 3 months follow

up

- EORTC-CIPN20 at baseline, before each oxaliplatin infusion and at 3 months

follow up

- EORTC QLQ-C30 at baseline and at 3 months follow up

Patient reported outcomes concerning sensory symptoms: at baseline, before and

after all cycles of oxaliplatin and at 3 month follow up

Result obtained from physical examination:

- Quantative sensory testing at baseline, before the fourth and eight oxaliplatin infusion and at 3 months follow up

- Clinical total neuropathy score at baseline, before the fourth and eight oxaliplatin infusion and at 3 months follow up

- Sock/glove lick distribution measured in centimeters of sensory symptoms (pinprick and cold) at baseline, before the fourth and eight oxaliplatin infusion and at 3 months follow up

- Time hand in ice-water at baseline and after the first oxaliplatin infusion

Results obtained from neurophysiologic studies

- Skin wrinkle at baseline, after the fourth and eight oxaliplatin infusion and at 3 months follow up

- Nerve conduction studies at baseline, after the fourth and eight oxaliplatin infusion and at 3 months follow up

- Surface EMG at baseline and after the first oxaliplatin infusion

Cumulative oxaliplatin dose at 3 months follow up

Analgesic usage at 3 months follow up

Study description

Background summary

Annually, 12700 patients are diagnosed with colon cancer in the Netherlands.
The number of annual colorectal cancer deaths is approximately half the annual

incidence. Colon cancer is after prostate cancer the most common type of cancer in men. In women, colon cancer takes a second place after breast cancer.
Of these patients, more than 50% will be treated with adjuvant chemotherapy after an operation in order to reduce the recurrence risk. Despite a curative treatment intention, an important part of the patients are faced with metastases, and either in this situation they will receive chemotherapy to extend life expectancy.
Oxaliplatin is a chemotherapeutic and the treatment of choice for many tumors of the gastro-intestinal tract. Up to 90% of these patients develop an acute neuropathy (i.e. a sodium channelopathy) as a result of the treatment with oxaliplatin. In the acute phase (during oxaliplatin treatment) patients experience intense pain and paresthesias in throat, face, hands and feet. In 25-30% of the patients, a chronic polyneuropathy (i.e. sensory neuropathy develops with continuous painful hands and feet leading to discomfort experienced by walking, holding cold things, or having difficulty with fine motor skills.
These neuropathic symptoms result in a substantial reduction in quality of life. The emergence of polyneuropathy seems to depend on the total administered dose oxaliplatin, severity of acute pain and patient (immunological and genetic) characteristics.
Medically, neuropathy is a reason to stop or reduce the dose of oxaliplatin. This can result in a reduced probability of curative adjuvant treatment; and in a reduced survival rate in case of oxaliplatin treatment for metastatic disease, because without oxaliplatin treatment options are less.
Despite extensive research, there is still no effective treatment for oxaliplatin-induced neuropathy; the usual analgesics (acetaminophen, NSAIDS, morphine) have little or no effect on the symptoms. Additionally, there are no known treatment options to prevent these symptoms.
Lidocaine is the only local anesthetic agent, considered safe for intravenous use. It has analgesic, antihyperalgesic and anti-inflammatory properties.
Limited research has revealed lidocaine to reduce pain in patients with chronic polyneuropathy. Proposed mechanisms are a direct effect of lidocaine on nerve fibers or/and modulation of the immune system. The pathophysiologic mechanism of oxaliplatin induced neuropathy are partially mediated via sodium- and potassium channels and via inflammatory mechanisms, which can be addressed by lidocaine.
We hypothesize that intravenous lidocaine reduces pain as a result of acute and subsequently chronic oxaliplatin induced neuropathy when administered simultaneously with oxaliplatin. Additionally we will investigate the acute inflammatory response in patients receiving oxaliplatin and lidocaine. Inflammatory factors play a role in pain transmission, we hypothesize lidocaine will modulate this.
Intravenous lidocaine administration during oxaliplatin treatment seems to be a very interesting, safe and low cost therapeutic option in the treatment of acute chemotherapeutic induced neuropathy, which additionally will lead to an improved oncologic treatment and improved quality of life of cancer patients. Moreover, several other chemotherapeutics (paclitaxel, vinca alkaloids,

bortezomib, cisplatin) are known for the development of neuropathy. The insights this (pilot) study will reveal, can be of particular interest to other patient groups

Study objective

Primary objective
To evaluate the efficacy of low dose intravenously lidocaine in comparison with placebo in terms of pain relief after the first oxaliplatin administration measured by a numeric rating scale (NRS 0-10).

Secondary objectives
1. Difference in pain scores between placebo and low dose intravenously lidocaine administered concomitant with oxaliplatin during and after all cycles of oxaliplatin administration.
2. Does low dose intravenously lidocaine administered concomitant with oxaliplatin attenuate systemic inflammatory response measured by plasma cytokine levels of interleukin (IL)-6, IL-8, IL-10, IL-1β, TNF-α and ICAM-1?
3. To evaluate if low dose intravenously lidocaine administered concomitant with oxaliplatin influences quantative sensory testing (pressure algometry and ice-bucket).
4. To evaluate if low dose intravenously lidocaine administered concomitant with oxaliplatin reduces chronic neuropathic changes measured by the clinical total neuropathy score (TNS), neurophysiologic conductions studies, and measured by a NCI-CTC and EORTC QLQ-CIPN20 questionnaire.
5. Cumulative oxaliplatin dosage.
6. Cumulative analgesics usage.
7. Other secondary outcomes consists of quality of life improvements measured by EORTC QLQ-C30 and patient reported outcome variables for sensory function.

On the basis of a review of the literature on pain measures prepared for the IMMPACT - II consensus meeting and discussions among the participants, an 11-point (ie 0-10) NRS measure of pain intensity is recommended as a core outcome measure in clinical trials of chronic pain treatments.

Reduction in pain intensity using the NRS is not the only clinical relevant measurement evaluating efficacy of pain treatment. Severity and consequences of the oxaliplatin induced neuropathy is another outcome. We propose this will be measured by the clinical total neuropathy score, quantitative sensory testing (pressure algometry), NCI-CTC questionnaire, EORTC QLQ-CIPN20 questionnaire, and neurophysiologic studies (skin wrinkle testing, nerve conduction studies, surface EMG and needle EMG if necessary), which are commonly used in other studies. Skin wrinkle testing is a reliable and efficient technique to detect small fiber neuropathy. Combining different measurements for detecting neuropathy and grading the severity of chemotherapy induced neuropathy is advised in literature.

Study design

This study will be a single center double blinded randomized placebo controlled trial

Intervention

Group I receives 1,5 mg/kg bolus of lidocaine intravenous 30 minutes before oxaliplatin administration followed by 1,5 mg/kg/h continuous infusion for 3 hours.
Group II receives saline in equivalent volumes.

Subjects will receive every oxaliplatin infusion the same study medication.

Study burden and risks

Subjects will be asked for NRS scores before, every hour during oxaliplatin administration and until 5 days after each oxaliplatin infusion (diary; pain scores of hand/feet, throat discomfort, muscle cramps, sensitivity to swallowing cold items and sensitivity touching cold items). During oxaliplatin administration and till 5 days afterwards patients will register sensory differences as a result of oxaliplatin.
During administration of the study medication subjects will be monitored respiratory and hemodynamically, to ensure possible side effects of lidocaine will be captured.
An additional intravenous line will be placed to administer lidocaine.
After the first oxaliplatin administration there will be an extra vena punction for blood samples to determine cytokine levels and RNA biobanking.
At baseline, before the fourth and eight oxaliplatin infusion and at 3 months follow up a clinical total neuropathy score and quantative sensory testing will be examined (30 min)
A NCI-CTC and EORTC QLQ-CIPN20 questionnaire will be performed at baseline, before each oxaliplatin infusion and at 3 months follow up (15min)
At baseline and at 3 months follow up a EORTC QLQ-C30 will be questioned (+/-10min).

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

Subjects with stage II to IV colorectal adenocarcinoma, who are scheduled to receive 6-8 cycles of oxaliplatin 130 mg/m2 every 3 weeks.

Exclusion criteria

Receiving other chemotherapeutics in medical history
Allergy to amide type of local anesthetics
Recent myocardial ischemia (<6 months)
Cardiale arrhytmias
Renal function disorders (MDRD < 60)
Liver failure (bilirubine >1,5x upper limit of normal)
Adequate hematologic parameters
Hypokaliemia
Pregnancy or lactating
Use of anti-arythmic drugs (flecainide)
Pre-existing form of neuropathy (polyneuropathy or small fibre neuropathy)
History of chronic pain and opioid use
Risk factors for CIPN: alcoholism, diabetes mellitus
No written informed consent by patient

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-06-2017
Enrollment:	24
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	21-09-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-01-2016
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-09-2016
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	EUCTR2015-002202-37-NL
CCMO	NL54639.091.15