A phase Ib/II study on the addition of Nab-paclitaxel (Abraxane) to capecitabine and oxaliplatin in the first-line treatment of metastastasized oesophagogastric carcinoma

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Primary objectivePhase 1: To assess the safety and tolerability of Nab-paclitaxel added to oxaliplatin and capecitabine at their currently optimal doses.Phase 2: To determine the anti-tumor activity of Nab-paclitaxel when co-administered with...

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

Summary

ID

NL-OMON44538

Source
ToetsingOnline

Brief title
ACTION

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
gastric cancer, oesophageal cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: capecitabine, nab-paclitaxel, oesophagogastric cancer, oxaliplatin

Outcome measures

Primary outcome

Phase 1: (dose limiting toxicity) and MTD (maximum tolerated dose) of

nab-paclitaxel co-administered with fixed doses of capecitabine and oxaliplatin

in patients with metastatic or irresectable carcinoma of the stomach or

oesophagus.

Phase 2: Progression free survival

Secondary outcome

Phase 1 1. Adverse events, serious adverse events according to NCI CTC version

4.0

2. Response rate according to RECIST 1.1

3. Progression free survival and overall survival

4. Self-reported neurotoxicity according to the EORTC QLQ CIPN2019

Phase 2 1. Adverse events, serious adverse events according to NCI CTC version

4.0

2. Response rate according to RECIST 1.1

3. Progression free survival and overall survival

4. Self-reported neurotoxicity according to the EORTC QLQ CIPN20

Study description

Background summary

Background
Esophagogastric cancer is a major cause of cancer related mortality, with an overall 5-year survival rate of 10% worldwide. The incidence of tumours of the oesophagus and cardia is rapidly increasing, mainly as the result of a marked increase in the incidence of adenocarcinoma. It ranks second of overall cancer incidence and mortality, and patients are often diagnosed with locally advanced or metastasized disease at first presentation. This group of patients has a dismal prognosis, with a median survival of less than a year, despite several extensive chemo- and chemoradiotherapy treatments.

Although oesophageal and gastric carcinomas may be regarded as two distinct entities with different etiologies (e.g. Barrett dysplasia due to acid reflux in oeosophageal cancer and chronic inflammation due to Helicobacter pylori infection) in gastric cancer - patients with metastasized adenocarcinoma of the esophagus, gastro-esophageal junction (GEJ) and stomach are often studied collectively, because the dysregulation of oncogenic pathways and the standard treatment do overlap.

For advanced oesophagogastric cancer fluoropyrimidines are the backbone of palliative chemotherapy and is commonly used in 2- or 3-drug combinations. The oral 5-FU analogues and prodrugs S1 and capecitabine have been shown to be (at least) equipotent to i.v. 5-FU.

In the western world, several fluoropyrimidine containing triplets have been used, such as 5- FU + doxorubicin + mitomycin (FAM), 5FU + doxorubicin + methotrexate (FAMTX), 5-FU + leucovorin + etoposide (ELF), 5-FU + epirubicin+cisplatin (ECF), 5-FU + mitomycin + cisplatin (MCF), and etoposide + doxorubicin + cisplatin (EAP). ECF was found to be superior compared with FAMTX in terms of survival and quality of life, although it should be noted that in this trial the control arm FAMTX performed poorly compared to other trials. Nevertheless, ECF has been regarded standard chemotherapy for advanced oesophagogastric cancer in different parts of the western world.

Currently, several new drugs have shown activity in oesophagogastric cancer, including docetaxel, irinotecan and oxaliplatin. The REAL-2 trial, aphase III trial testing oxaliplatin and capecitabine in a 2 × 2 design, has shown that the overall survival was non-inferior in patients treated with oxaliplatin combinations compared with cisplatin combinations in advanced oesophago-gastric

cancer. The EOX regimen was superior to the ECF regimen in terms of overall survival (median 11.2 versus 9.9 months, HR 0.8 95% CI 0.65-0.97).3 A randomized phase III trial comparing docetaxel + cisplatin + 5-FU (DCF) versus 5-FU + cisplatin (FP) (11), confirmed a significant advantage for DCF compared to FP in terms of overall survival (9.2 months versus 8.6 months). However, the addition of docetaxel has led to increased toxicity, with more neutropenia and diarrhoea seen in patients treated with DCF compared to FP, although quality of life was reported better in the DCF arm.
In general, triplets have lead to modestly increased response rates and survival, but at the cost of increased toxicity. In fact, sequential use of doublets and singlets may achieve a better therapeutic index than first-line use of three drugs. However, in clinical practice after progression on first line therapy, a substantial number of oesophagogastric cancer patients may not be able to start second line chemotherapy due to rapid clinical deterioration. Therefore, new triplets with high anti-tumor activity and low toxicity are urgently needed.

Rationale for the study
Given the activity of capecitabine and oxaliplatin containing regimens and the potential of taxanes in oesophagogastric cancer, we propose a phase I study combining capecitabine and oxliplatin with Nab-paclitaxel. Solvent-based taxanes (paclitaxel, docetaxel) can cause severe toxicities not only by the active agents itself but also by the solvents like cremophor. Nab-paclitaxel (Abraxane) is a solvent-free formulation of paclitaxel encapsulated in albumin. It does not require premedication with corticosteroids or antihistamines to prevent the risk of solvent-mediated hypersensitivity reactions. This new formulation improves safety profile, allows higher dosing with shorter infusion duration, and produces higher tumor drug concentration. It has proven activity in breast cancer, non small lung cancer and pancreatic cancer, as well as in gastric cancer models.

Study objective

Primary objective
Phase 1: To assess the safety and tolerability of Nab-paclitaxel added to oxaliplatin and capecitabine at their currently optimal doses.

Phase 2: To determine the anti-tumor activity of Nab-paclitaxel when co-administered with oxaliplatin and capecitabine in patients with irresectable or metastasized oesophagogastric cancer in terms of progression free survival.

Secondary objectives
Phase 1: 1. To assess the number of complete cycles of Nab-paclitaxel, oxaliplatin and capecitabine delivered.
2. To assess response rate, progression free survival, overall survival.
3. To assess self-reported neurotoxicity.

Phase 2: 1. To assess the number of complete cycles of Nab-paclitaxel, oxaliplatin and capecitabine delivered.
2. To assess response rate, overall survival.
3. To assess self-reported neurotoxicity.

Study design

This is a single-center, open label, dose finding, phase I/II study.

Intervention

In the phase I part of the study, the dose of nab-paclitaxel in combination of capecitabine and oxaliplatin will be escalated in fixed increments according to the dose escalation scheme outlined below

doselevel nab-paclitaxel day 1and 8 capecitabine twice daily for 14 days oxaliplatin day 1 and 8 minimal number of patients
-1 40 mg/m2 1000 mg/m2 65 mg/m2 -
1 (start) 60 mg/m2 1000 mg/m2 65 mg/m2 3
2 80 mg/m2 1000 mg/m2 65 mg/m2 3
3 100 mg/m2 1000 mg/m2 65 mg/m2 3
4 120 mg/m2 1000 mg/m2 65 mg/m2 3

Once the maximum tolerated dose (MTD) for the combination therapy has been determined, 6 up to 14 additional patients will be enrolled in this part of the study to further evaluate safety and tolerability (i.e. in total 20 patients will be treated at the recommended phase 2 dose before proceeding to phase II, in case of unacceptable toxicity the investiagator can decide to lower the doselevel and re-determine the MTD)

In the phase II part of the study the maximum tolerated dose from the phase I part of the study will be used in combination with fixed dosages of capecitabine and oxaliplatin; nab-paclitaxel day 1 and 8 according to the MTD of the phase 1 part of the study combined with capecitabine for 14 days at 1000mg/m2 twice daily and oxaliplatin day 1 and 8 65mg/m2.

Study burden and risks

By participating in this study, additional research on tumor material available in the pathology archives at the AMC will be done. If this material is not (sufficiently) present, an additional biopsy will have to be taken.
Before conducting any additional biopsy, the patient will have to come to the hospital. Before the biopsy is taken, the skin is numbed. The taking of biopsies is then virtually painless and safe. However, there is a slightly increased risk of the occurrence of bleeding.

Subsequently, nab-pacitaxel is administered intravenously in combination with oxaliplatin on day 1 and day 8 of a three-weekly cycle, and during day 1-14, capecitabine tablets will be taken. Prior to treatment, during treatment and after treatment additional blood is collected.
We will also ask to complete the quality of life questionnaire before initiation of treatment, after three weeks, after nine weeks, and then every nine weeks.

Several side effects of nab-paclitaxel have preiously been reported, first important to mention is neurotoxicity. Other possible side effects are nausea / vomiting, and diarrhea, mouth sores, loss of appetite, muscle pain, joint pain, hair loss, rash, acute hypersensitivity reactions during the running of the medication through the IV and bone marrow suppression.

The occurrence of other or serious side effects as a result of the combined administration of the three medications nothing is known because this has never been done before.

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

1. Male or female >= 18 year ;2. Histological proof of metastastic or irresectable carcinoma of the stomach or oesophagus.;3. WHO 0-2.;4. Measureable/evaluable disease as assessed by RECIST 1.1;5. Adequate bone marrow and organ function.;6. Informed consent.

Exclusion criteria

1. Prior systemic treatment for metastatic or irresectable stomach or oesophageal cancer;2. All target lesions in a radiation field without documented disease progression,Palliative radiotherapy on the primary tumor or a metastastic lesion is allowed if other untreated lesions for evaluation are present.;3. WHO 3-4.;4. Use of other investigational drugs within 30 days of enrollment or 5 half-lives of the study drug, whichever is longer.;5. CNS metastases or a CNS malignancy.;6. Other previous malignancies except cervical carcinoma and squamous carcinoma of the skin >= 5 years ago

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-11-2014
Enrollment:	154
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nab-paclitaxel
Generic name:	Abraxane
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	23-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	16-10-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	29-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	11-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	03-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2016
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	EUCTR2014-001333-88-NL

Register	ID
CCMO	NL49837.018.14