Simultaneous Integrated Boost Radiation Therapy with concomitant Capecitabine and Mitomycin-C chemotherapy for locally advanced Anal Carcinoma

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Primary objective of the study is the assessment of the dose limiting toxicity (DLT) and the maximal tolerated dose (MTD) of capecitabine and mitomycin-C with concomitant SIBRT in patients with locally advanced anal carcinoma.Secondary objectives...

Ethical review	Approved WMO
Status	Pending
Health condition type	Anal and rectal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON31876

Source
ToetsingOnline

Brief title
SIBRT, capecitabine and mitomycin-C for locally advanced anal carcinoma

Condition

- Anal and rectal conditions NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Anal carcinoma, cancer of the anus

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: afdelingsbudget

Intervention

Keyword: anal cancer, capecitabine, radiotherapy, SIBRT

Outcome measures

Primary outcome

Assessment of the MTD and DLT of SIBRT in combination with capecitabine in

mitomycine-C for the treatment of locally advanced anal carcinoma.

Secondary outcome

Assessment of the:

- preliminary clinical activity

- pharmacokinetics

- pharmacogenetics

- HPV status

Study description

Background summary

Until three decades ago, the treatment of anal cancer consisted of abdominoperineal resection resulting in a permanent colostomy. This rather inconvenient approach has been substituted now for a combined modality treatment of radio- and chemotherapy. In general treatment nowadays consists of radiotherapy of 45 - 50.4 Gy over 4 - 5 weeks (± boost), with a continuous infusion of 1000 mg/m2 5-FU for 4 days or 750 mg/m2 for 5 days in the first and last week of radiotherapy, with/without mitomycin-C 10 - 15 mg/m2 on day 1 on the first and/or second course. This leads to a complete remission rate of about 80% of the patients and the disease-free survival of 50% after 4 years. Capecitabine is the oral prodrug of 5-FU and is approved for the first-line treatment of metastatic colorectal carcinoma and for the treatment of advanced

breast cancer and gastric cancer.
Furthermore, several studies have shown that capecitabine is a convenient treatment alternative for 5-FU in the treatment of rectal cancer, with treatment consisting of the combination of radiotherapy and capecitabine (5 - 7 days a week), similar to the proposal in this study protocol. Therefore, replacement of 5-FU by capecitabine seems also an attractive alternative in the treatment of patients with locally advanced cancer of the anal canal, which would make the treatment much more convenient for these patients rather than the protracted venous infusion of 5-FU. It enables continuous administration during the whole treatment period with radiotherapy.
Radiation dose and schedule are of importance for treatment outcome in anal cancer. Dose-limiting toxicity is often skin and bone marrow toxicity. For this reason, split dose radiation schedules have been developed, which have an unfavourable influence on outcome. A promising approach is the use of newer techniques such as SIBRT, which permits treatment of anal cancer without interruption of radiotherapy.

Study objective

Primary objective of the study is the assessment of the dose limiting toxicity (DLT) and the maximal tolerated dose (MTD) of capecitabine and mitomycin-C with concomitant SIBRT in patients with locally advanced anal carcinoma.

Secondary objectives are:
- To determine preliminary clinical activity (response rate, time to progression) of SIBRT with concomitant capecitabine and mitomycin-C in patients with locally advanced AC
- To determine the pharmacokinetics of capecitabine and mitomycin-C with concomitant SIBRT
- To establish the effect of functional genetic polymorphisms of the drug metabolizing gene DPYD and target gene TS on the pharmacokinetics and pharmacodynamics of capecitabine and mitomycin-C with concomitant SIBRT
- To assess the prevalence of HPV in this patient population
- To determine the type of the HPV in HPV-positive patients

Study design

This is a non-randomized, multi-center, dose-escalating, phase I study, to assess the safety, maximum tolerated dose and pharmacokinetics of capecitabine and mitomycin-C with concomitant SIBRT in patients with locally advanced anal carcinoma.
Patients who meet the eligibility criteria will be treated according to study protocol, starting with the first 3 patients at the lowest dose level, i.e. dose level 1. In total, 3 dose levels are defined. Entering of patients in subsequent dose levels will proceed until DLT and MTD are assessed. Additionally, the pharmacokinetics and - genetics will be assessed, and

tumormaterial will be analyzed to assess the prevalence and type of HPV in this patient population.

Intervention

Treatment consists of:
- SIBRT 5 days a week (Monday - Friday) for 6 * weeks, i.e. 33 x 1.8/1.5 Gy (± 3 x 1.8 Gy boost)
- Capecitabine po BID 5 days a week (Monday - Friday) for 6 * weeks
- Mitomycin-C 10 mg/m2 (with a maximum of 15 mg) as intravenous bolus injection on day 1

Radiotherapy will start 2 ± 1 hours after the morning dose of capecitabine.

3 dose levels are defined. Only the dose of capecitabine will be escalated from 500 to 650 and 825 mg/m2 twice daily in dose levels 1, 2 and 3, respectively. The dose of mitomycine-C is in all dose levels 10 mg/m2 (max 15 mg), and the radiation dose is 33 x 1.8/1.5 Gy (± 3 x 1.8 Gy boost).

The first 3 patients will start in dose level 1. If no dose-limiting toxicity is observed 2 weeks after end of treatment of these 3 patients at that dose level, the next three patients may proceed to dose level 2. The same accounts for the proceeding to dose level 3. No intrapatient dose escalation will be applied.
If at any dose level one of the 3 patients develops dose-limiting toxicity, up to an additional 3 patients (up to a total of 6) will be treated at the same dose level. If 2 or more out of 6 exhibit DLT, the maximum tolerated dose (MTD) will be considered to be the dose given at the previous lower dose level. This will be the advised dose for capecitabine and mitomycin-C given with concomitant SIBRT in patients with locally advanced AC. Finally, a total of 8 patients will be treated at the MTD.

Study burden and risks

Blood sampling procedures are planned on day 1, which is associated with a minimal risk.

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. Patients with histologically or cytologically confirmed primary advanced anal carcinoma with tumor (T), nodal (N) and metastases (M) stage:
- T2 (>4 cm) - T3 - T4 / N0 - 1 / M0
- T1 - 4 / N2 - 3 / M0
2. Previous (neo)adjuvant chemotherapy > 12 months ago is allowed. Otherwise patients should be chemonaive.
3. Measurable or evaluable non-measurable disease
4. Age 18 years or older
5. Able to swallow and retain oral medication
6. Able and willing to undergo blood sampling for pharmacokinetic and pharmacogenetic analysis
7. Life expectancy of at least 3 months allowing adequate follow up of toxicity evaluation and antitumor activity
8. Minimal acceptable safety laboratory values defined as:
a) ANC >= 1.5 x 10**9/L
b) Platelet count >= 100 x 10**9/L
c) Haemoglobin level >= 6.0 mmol/l or higher - prior transfusion is permitted
d) Hepatic function as defined by serum bilirubin 1.5 x ULN or less, ALT and AST and alkaline phosphatase 2.5 x ULN or less
e) Renal function as defined by serum creatinine <= 1.5 x ULN or creatinine clearance >= 50

ml/min (by Cockcroft-Gault formula).
9. Able and willing to give written informed consent
10. WHO performance status of 0 - 2

Exclusion criteria

1. Known CNS or leptomeningeal metastases (a CT or MRI scan should be done if there is a clinical suspicion of CNS metastases)
2. History of another metastasized cancer less than 5 years ago
3. Uncontrolled infectious disease or known hepatitis B or hepatitis C patients
4. HIV patients treated with HAART
5. Previous radiotherapy to the pelvic and/or unguinal region
6. Uncontrolled cardiovascular disease
7. Previous severe fluoropyrimidine toxicity
8. DPYD*2A mutation present
9. Patients with known alcoholism, drug addiction and/or psychotic disorders in the history that are not suitable for adequate follow up
10. Women who are pregnant or breast feeding
11. Women of childbearing potential who refuse to use a reliable contraceptive method throughout the study
12. Any other medical condition that would interfere with study procedures and/or decrease safety of the protocol treatment

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2007
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Mutamycin
Generic name:	Mitomycin-C
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	Capecitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-11-2007
Application type:	First submission
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	EUCTR2007-005897-30-NL
CCMO	NL20249.031.07