Pre-operative Decitabine in Colon Cancer: a proof of principle study

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

Summary

ID

NL-OMON41603

Source
ToetsingOnline

Brief title
DECO

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
colon cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: KWF kankerbestrijding

Intervention

Keyword: colon cancer, decitabine, methylation

Outcome measures

Primary outcome

The primary study parameter is Wnt target gene expression (APCDD1, AXIN2, DKK1,

LGR5 and ASCL2).

Secondary outcome

Secondary study parameters are Wnt target and CIMP gene methylation,

beta-catenin localization, proliferation (Ki-67), apoptosis (TUNEL and M30

assay) and tumor differentation.

Study description

Background summary

Colon cancer is the second leading cause of cancer-related death world wide. Although patients presenting with early disease (stage I-III) can be cured, prognosis varies from 90% in stage I to 50-80% in stage II and III. Therefore, prevention of metastases after early disease is of utmost importance. Extensive studies of the Wnt signal cascade have elucidated its role in colorectal cancer development and proliferation. Several well-known targets of the Wnt-cascade, like DKK1, APCDD1 and AXIN2, serve as feedback inhibitors and likely prevent pathway hyperactivation. Therefore, loss of these control mechanisms, for example due to repression of Wnt targets by CpG island methylation, serves as a potent proliferative signal. Recently, we identified a subset of colon cancers that are typified by CpG island methylation of specific Wnt target genes and have a poor prognosis. Moreover, in preclinical studies we showed that derepression of Wnt-targets by the demethylating agent decitabine resulted in tumor growth suppression. Thus, derepression of Wnt targets may provide a novel target for therapy.

Study objective

The primary objective of the study is to assess in patients with primary colon cancer whether short-course pre-operative treatment with decitabine can

increase Wnt target gene expression as measured in resected tumors compared to pretreatment biopsies. The secondary objective of the study is to assess in patients with primary colon cancer whether short-course pre-operative treatment with decitabine can revert CpG methylation and induce more favorable tumor characteristics as measured in resected tumors compared to pretreatment biopsies. The tertiary objective is to compare changes in Wnt target gene expression, CpG methylation and tumor characteristics for Wnt methylated and non-methylated tumors as measured in resected tumors compared to pretreatment biopsies and identify new stratification markers.

Study design

Interventional study.

Intervention

In patients with proven colon cancer, five extra biopsies during planned endoscopy will be taken from the tumour during endoscopy to determine CpG methylation of Wnt target genes in fresh tumor samples. Otherwise, tumor material obtained during previous endoscopy will be used. Next, these patients will pre-operatively receive decitabine as an intravenous infusion at a dose of 25 mg/m2 over 1 hr on two consecutive days. After resection, Wnt target gene expression and CpG methylation of Wnt target genes will again be determined in tumor samples.

Study burden and risks

Patients undergoing extra biopsies during endoscopy have a very small additional risk of intestinal bleeding and perforation. Patients who are treated with decitabine have a risk of experiencing decitabine induced side effects, including neutropenia, anorexia and fatigue.

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

In order to participate in the first part of the study, determination of methylation status on tumor biopsies, a subject must meet all of the following criteria:
1. Biopsy proven colon cancer or high suspicion of colon cancer.
2. Age >= 18yr.
3. Written informed consent.;In order to participate in the second part of the study - treatment with decitabine - a subject must meet all of the following criteria:
1. Patients with biopsy proven colon cancer who will undergo primary tumor resection.
2. Age >= 18yr.
3. ECOG/ WHO performance 0-2.
4. Adequate bone marrow function (ANC>1500/mm3, hemoglobin>9g/dL (which may be obtained by transfusions), platelets>100,000)
5. Adequate hepatic function (AST and ALT <2.5x upper limit of normal (ULN)).
6. Adequate renal function (Serum creatinine <=1.5 x ULN or calculated creatinine clearance of >50ml/min)
7. Women of child-bearing age must be willing to use adequate contraception and have negative serum or urine pregnancy test within 3 days prior to registration.
8. Written informed consent.;In order to participate part IIB of the study - obtaining tumor material - a subject must meet all of the following criteria:
1. Patients with biopsy proven colon cancer who will undergo primary tumor resection.
2. Age >= 18yr.
3. Karnofsky Performance Score 70.
4. Written informed consent.

Exclusion criteria

A potential subject for the first part of the study - determination of methylation status on tumor biopsies - who meets any of the following criteria will be excluded from participation in this study:
1. Any psychological, familial, sociological or geographical condition potentially hampering adequate informed consent or compliance with the study protocol.;A potential subject for the second part of the study - treatment with decitabine - who meets any of the following criteria will be excluded from participation in this study:
1. Known hypersensitivity to decitabine or its additives.
2. Surgery not planned according to time frame of the study,
3. Other systemic or local treatment of the primary tumor in the waiting time until surgery.
4. Administration of any experimental drug within 60 days prior to the first dose of decitabine.
5. Women of child-bearing age who are pregnant or lactating.
6. Sexual active males who have intercourse with women of child-bearing age and do not take adequate contraceptive measures.
7. Any psychological, familial, sociological or geographical condition potentially hampering adequate informed consent or compliance with the study protocol.;A potential subject for part IIB of the study - obtaining tumor material - who meets any of the following criteria will be excluded from participation in this study:
1. Surgery not planned according to time frame of the study
2. Other systemic or local treatment of the primary tumor in the waiting time until surgery.
3. Any psychological, familial, sociological or geographical condition potentially hampering adequate informed consent or compliance with the study protocol.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-02-2014

Enrollment:	88
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-04-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	07-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2016
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	EUCTR2013-001060-38-NL
ClinicalTrials.gov	NCT01882660
CCMO	NL44048.018.13