Dendritic cell vaccination in patients with Lynch Syndrome or colorectal cancer with MSI

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON39056

Source
ToetsingOnline

Brief title
DC vaccination in lynch syndrome patients

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Malignant and unspecified neoplasms gastrointestinal NEC
- Miscellaneous and site unspecified neoplasms benign

Synonym
hereditary non-polyposis colorectal cancer, Lynch syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: DC vaccination, frame shift-derived neopeptides, immune therapy, lynch syndrome

Outcome measures

Primary outcome

The first objective of this study is to evaluate safety and feasibility of

vaccination with frameshift-derived neoantigen-loaded DC.

Secondary outcome

The secondary objectives of the study are to evaluate whether peptide-loaded DC

can induce or enhance an immune response to tumor-associated antigen CEA and

specific frameshift-derived neoantigens in the study population and the

pathological and or clinical responses, e.g. disease-free survival, determined

according to the standard protocol.

Study description

Background summary

Ex vivo generated and tumor-antigen-loaded dendritic cells (DC) are currently used in clinical vaccination protocols in cancer patients. DC vaccines are safe, with minimal side effects. Evaluating more than 200 patients treated the past ten years we found that clinical responses measured in several patients directly coincide with specific cytotoxic T cell responses. The majority of studies investigated the therapeutic effects of DC vaccines in late-stage cancer patients with metastasis. In these (heavily) pretreated patients the immune system is compromised. Based on our observations that a specific immune response is indicative for a good clinical outcome we believe that the full potential of these immunostimulatory cells has to be exploited in high-risk patients with low tumor burden or in a precancerous state.
A good clinical model are carriers of a germline mutation in one of the DNA mismatch repair (MMR) genes, such as patients with Lynch syndrome (also known

as Hereditary Non-Polyposis Colorectal Cancer or HNPCC). These persons have a lifetime risk of 60-80% for colorectal cancer that has developed within a few years develops from a precancerous adenoma. The immune system is thought to be of potential great importance as the colorectal cancer in Lynch syndrome is characterized by a strong lymphocyte infiltration, even at he stage of adenomas. In affected cancer lesions, MMR dysfunction results in frameshift mutations at short, repetitive DNA sequences referred to as microsatellites. In coding regions these mutations destroy gene function and have been demonstrated to lead to the production of neopeptides [9]. These neopeptides are 1) tumor specific, because frameshift mutations only occur in tumor cells and their premalignant progenitors and 2) immunogenic, since cytotoxic T cells (CTL) and helper T cells could be induced in vitro from blood of patients with Lynch syndrome. Similar mechanisms occur in sporadic colon cancer with MMR dysfunction, which represents about 10-15% of all colorectal cancers.

Study objective

The primary objective is the safety and feasibility of CEA/frameshift derived neopeptide loaded DC in patient with MSI-positive colorectal cancer and persons who are known to be carrier of a germline MMR-gene mutation with no signs of disease yet.
The secondary objectives of the study are to evaluate whether peptide-loaded DC can induce or enhance an immune response to tumor-associated antigen CEA and specific frameshift-derived neoantigens in the study population and the pathological and or clinical responses, e.g. disease-free survival, determined according to the standard protocol.

Study design

This study is an open label phase I/II study.

Intervention

Treatment of subjects
Curative: MMR mutation carriers with CRC (group I)
MMR-gene mutation carriers with a carcinoma will be asked to participate in this study. HLA-A2.1 positive CRC patients will be vaccinated 3 times every week with DC loaded with CEA-derived and frameshift mutation-derived neopeptides. All DC will be pulsed with KLH as an immune control. DC will be simultaneously administered intradermally (i.d.) in the upper leg and intravenously (i.v.) 10 and 20 x 106 cells, respectively. After the 3 vaccinations a DTH will be performed, from which biopsies will be taken for T cell analysis. If no relapse occurs, we will repeat this cycle two more times with a 6 months interval. Thereafter, patients will be scheduled for regular follow-up and will receive surveillance colonoscopy every 1-2 years.
Preventative: MMR mutation carriers with no signs of disease (group II)

These healthy individuals will be treated with DC loaded with frameshift mutation-derived neopeptides and with DC loaded with CEA, as described above for group I, 5-6 weeks prior to the regularly scheduled surveillance colonoscopy, with regular follow up and surveillance colonoscopy every 1-2 years. If no carcinomas are developed, we will repeat this cycle two more times with a 6 months interval.

Study burden and risks

Based on our experience with peptide-pulsed DC, we expect that these DC will be well tolerated. Common and expected side effects of DC vaccination are usually mild and include flu-like symptoms and local reaction at injection site, both common toxicity criteria (CTC) grade 1.
Patient material that will be requested during the study in addition to standard procedures is summarized in the table below.

Day Event
Patient material
-21 to -28 Inclusion (HLA-typing, virus testing) 30 ml blood
-9 Apheresis
Mononuclear cells, 5 ml serum
0 DC vaccination I i.d./i.v. 1 skin biopsy
7 DC vaccination II i.d./i.v. 80 ml heparin
blood, 5 ml serum
14 DC vaccination III i.d./i.v. 80 ml heparin
blood, 5 ml serum
19 DTH 90
ml heparin blood, 5 ml serum
21 Biopsies of DTH lesions 4 + 1 (=control) skin
biopsies

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

* histologically documented evidence of CRC (group I) and Lynch syndrome carrier without signs of disease (group II)
* HLA-A2.1 phenotype is required
* MSI high tumor
* WBC >3.0×109/l, lymphocytes >0.8×109/l, platelets >100×109/l, serum creatinine <150 µmol/l, serum bilirubin <25 µmol/l
* WHO performance status 0-1 (Karnofsky 100-70%)
* age 18-75 years
* expected adequacy of follow-up
* written informed consent

Exclusion criteria

* history of malignancy in the past 5 years with the exception of adequately treated basal cell carcinoma of the skin or carcinoma in situ of the cervix
* serious active infections, HbsAg or HIV positive
* autoimmune diseases or organ allografts
* concomitant use of immunosuppressive drugs
* known allergy to shell fish
* pregnant or lactating women

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-12-2010
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	21-01-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-02-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-05-2010

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-11-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-08-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2008-005584-33-NL
CCMO	NL28985.000.09