Dendritic cell-based immunotherapy combined with low-dose cyclophosphamide in patients with malignant pleural mesothelioma

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Ethical review	Approved WMO
Status	Pending
Health condition type	Pleural disorders
Study type	Interventional

Summary

ID

NL-OMON32554

Source
ToetsingOnline

Brief title
DC-immunotherapy and cyclophosphamide in treating mesothelioma

Condition

- Pleural disorders

Synonym
mesothelioma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Asbestkanker

Intervention

Keyword: Cyclophosphamide, Dendritic cells, Immunotherapy, Mesothelioma

Outcome measures

Primary outcome

To define the safety and toxicity of tumor lysate-pulsed dendritic cells (DCs)

combined with a low dose cyclophosphamide in patients with malignant pleural

mesothelioma

Secondary outcome

To determine if vaccination with DCs results in a detectable immune response

To determine if low-dose cyclophosphamide leads to a decrease in regulatory T

cells in the blood of patients

To observe and document anti-cancer activity by clinical evaluation (CT-scan)

Study description

Background summary

Cancer immunotherapy attempts to harness the exquisite power and specificity of the immune system to recognize and destroy tumor cells or to prevent tumor recurrence. The fact that some patients with malignant pleural mesothelioma (MM) have tumors that regress spontaneously or respond to immunotherapy suggests that the immune system can generate anti-tumor reactivity under some circumstances. One such cancer immunotherapy approach uses the patients* own dendritic cells (DCs) to present tumor-associated antigens and thereby generate tumor-specific immunity. DCs are extremely potent antigen presenting cells specialized for inducing activation and proliferation of lymphocytes essential for tumor killing. If the DCs can be made to attack mesothelioma cells, it would mean a non-toxic treatment (unlike chemo- and radiotherapy) with minor side-effects, and long-lasting immunological memory (similar to vaccines providing long-term protection against viruses). Several studies in other

cancers in humans, e.g. renal cell carcinoma, melanoma, glioma and lung cancer, have shown that DC-based immunotherapy can induce tumor-specific cytotoxic T lymphocyte (CTL) responses that lead to shrinkage of the tumor and sometimes prolonged survival. However, tumors frequently interfere with the development and function of immune responses and can actively down-regulate anti-tumor immunity. With increasing knowledge of the basic aspects of tumor immunology, immunotherapy might hold the key to the clinical realization of effective therapeutic treatment for mesothelioma.

The results from the phase I study (MEC-2005-269) showed that injection of DCs was overall well tolerated without systemic toxicity, with the exception of a low-grade flu-like symptoms: fever, rigors (chills), and a temporarily local skin reaction after DC injection (mild grade 1 or 2) (appendix 1). Local accumulation of CD4+ and CD8+ T cells were found at the vaccination sites. Body temperature was increased in 5 patients but did not exceed 39*C mainly after the second and third vaccination. All participants thus far experienced no rash or lymphadenopathy or developed any clinical evidence of autoimmunity or rheumatoid disease. DTH and strong antibody immune responses (IgM and IgG) on KLH were seen in all patients indicating that immune responses were generated. CT scans and X-rays from a few patients revealed small to substantial regressions of the tumor during the DC treatment.

Study objective

We expect to finalize the current phase I study by the May 2008 demonstrating that injection of tumor lysate-pulsed autologous DCs injected in patients with MM after chemotherapy is safe and well tolerated with induction of immune responses. New insights have anticipated that better effects may be achieved by perfecting the strategy by depleting regulatory T cells (Tregs) using low-dose cyclophosphamide in order to improve the anti-tumor immune responses elicited by DC vaccines (preliminary studies im mice from our group have demonstrated this). In the here proposed phase I clinical trial, ten patients will be treated with DC vaccination plus cyclophosphamide after chemotherapy (appendix 3).

Study design

Ten patients are receive DC vaccination in conjunction with low-dose cyclophosphamide. Cyclophosphamide (Endoxan) will be taken orally the week proceeding (week 22), the weeks in between (week 24, 26), and one week after (week 28) the DC vaccinations. The dose is 100 mg (two [2] tablets)/day. The patient will take medication 2 hours after breakfast. The subject will be asked to increase their fluid intake by extra drinking water or other non-caffeinated beverage throughout the day. This dose is well tolerated without toxicity.

We want to emphasize that no changes will be made in preparing and loading of

dendritic cells, dosing, timing, and schedule (or other variables) compared to the phase I study.

Intervention

Ten patients will be treated with DC immunotherapy (3 times with 2-weekly interval). In de time inbetween an oral administration of one tablet of cyclophosphamide is taken with a large amount of water (4 x 7 days, 1 tablet daily).

Study burden and risks

All extra examinations for patients are performed by qualified personnel and according to appropriate rules.
MEC-2005-269 has shown that the risks associated with the injection of dendritic cells is minimal (appendix 1). The results from this study showed that injection of dendritic cells was overall well tolerated without systemic toxicity, with the exception of a low-grade flu-like symptoms: fever, rigors (chills), and a temporarily local skin reaction after DC injection (mild grade 1 or 2). Local accumulation of CD4+ and CD8+ T cells were found at the vaccination sites. Body temperature was increased in 5 patients but did not exceed 39*C mainly after the second and third vaccination. All participants thus far experienced no rash or lymphadenopathy or developed any clinical evidence of autoimmunity or rheumatoid disease. DTH and strong antibody immune responses (IgM and IgG) on a model antigen (KLH) were seen in all patients indicating that immune responses were generated.
However during the whole procedure, several punctures are necessary and are considered as (average) painful. First, the apheresis method is based on blood being drawn from one vein and returned to another vein continuously, normally using a vein in both arms, whilst the blood is processed with a view to monocyte extraction, in the machine. The collection of cells, takes 3 to 4 hours, having to keep the elbow stretched and immobilized for so long can be quite uncomfortable and sometimes even painful for the patient or donor. However, this procedure takes place under strict guidance of the department of Hematology (years of experience). Second, a skin test is performed in which small volumes (max. 50 ul) of cells or antigens are injected in the skin of the lower arm to induce a delayed type hypersensitivity test. Furthermore, venapunctures are performed bi-weekly to determine the side-effects and efficacy of dendritic cell immunotherapy in patients.
The adaptation in this amendment compared to MEC-2005-269 is the oral intake of cyclophosphamide in the weeks in between dendritic cell vaccination.

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

As for our earlier study (MEC-2005-269):;Patients with clinically and histological or cytological confirmed newly diagnosed mesothelioma, that can be measured in two dimensions by a radiologic imaging study.
Patients must be at least 18 years old and must be able to give written informed consent.
Patients must be ambulatory (Karnofsky scale > 70, or WHO-ECOG performance status 0,1, or 2) and in stable medical condition. The expected survival must be at least 4 months.
Patients must have normal organ function and adequate bone marrow reserve: absolute neutrophil count > 1.5*109/l, platelet count > 100*109/l, and Hb > 6.0 mmol/l.
Positive delayed type hypersensitivity skin test (induration > 2mm after 48hrs) against at least one positive control antigen of MULTITEST CMI (Pasteur merieux).
Stable disease or response after chemotherapy.
Availability of sufficient tumor material of the patient.
Ability to return to the Erasmus MC for adequate follow-up as required by this protocol. ;New for this study (in comparison to MEC-2005-269) are:
Able to tolerate oral therapy

No impairment of gastrointestinal (GI) function or GI disease that may affect or alter absorption of cyclophosphamide (e.g., mal-absorption syndrome, history of total gastrectomy/significant small bowel resection)
No history of allergic reactions (>= grade 3 or 4) to compounds of similar chemical or biologic composition to cyclophosphamide (i.e., alkylating agents)
No known intolerance or hypersensitivity reaction to cyclophosphamide

Exclusion criteria

As for our earlier study (MEC-2005-269):;Conditions that make the patient unfit for chemotherapy or progressive disease after 4 cycles of chemotherapy.
Pleurodesis at the affected side before the pleural fluid is obtained.
Medical or psychological impediment to probable compliance with the protocol.
Patients on steroid (or other immunosuppressive agents) are excluded on the basis of potential immune suppression. Patients must have had 6 weeks of discontinuation and must stop of any such treatment during the time of the study.
No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, superficial or in-situ cancer of the bladder or other cancer for which the patient has been disease-free for five years.
Serious concomitant disease, no active infections. Patients with a history of autoimmune disease or organ allografts, or with active acute or chronic infection, including HIV and viral hepatitis.
Patients with serious intercurrent chronic or acute illness such as pulmonary (asthma or COPD) or cardiac (NYHA class III or IV) or hepatic disease or other illness considered by the study coordinators to constitute an unwarranted high risk for investigational DC treatment.
Patients with a known allergy to shell fish (contains KLH).
Pregnant or lactating women.
Patients with inadequate peripheral vein access to perform leukapheresis
Concomitant participation in another clinical trial
An organic brain syndrome or other significant psychiatric abnormality which would comprise the ability to give informed consent, and preclude participation in the full protocol and follow-up.
Absence of assurance of compliance with the protocol. Lack of availability for follow-up assessment. ;No additiona exclusion criteria in comparison to MEC-2005-269

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2009
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	Endoxan
Generic name:	cyclophosphamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	16-01-2009
Application type:	First submission
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

ID: 24867
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
Other	00280982
EudraCT	EUCTR2008-000957-36-NL
CCMO	NL24050.000.08
OMON	NL-OMON24867