A phase I study on Dendritic cells loaded with allogeneous cell lysate (Alloys) in patients with mesothelioma as maintenance treatment (AlloDen)

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The objective of the present trial is to investigate the safety of an allogenic tumor cell lysate loaded onto autologuous dendritic cells (AlloDen) in patients with malignant mesothelioma (MM). Heretoo we will perform a phase I study with a…

Ethical review	Approved WMO
Status	Pending
Health condition type	Mesotheliomas
Study type	Interventional

Summary

ID

NL-OMON41650

Source
ToetsingOnline

Brief title
AlloDen1

Condition

- Mesotheliomas

Synonym
asbestos cancer, 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,zonmw subsidie aangevraagd,Amphera b.v.

Intervention

Keyword: dendritic cell, immunotherapy, mesothelioma

Outcome measures

Primary outcome

The aim of this phase I protocol is to study the toxicity and safety of AlloDen

(DC-based immunotherapy) in MM patients. Toxicities will be scored according to

CTC criteria version 4.0. The following toxicities occurring during 8 weeks

after the first vaccination, will be considered as dose-limiting (DLTs):

Hematological:

Thrombocytopenia grade 3 during longer then 7 days or grade 4

Neutropenia grade 3 during longer then 7 days or grade 4

Non-hematological:

Any grade 3/4 toxicity except for diarrhea, nausea, vomiting, hypertension if

not adequately treatable, skin toxicity.

Immune related:

Any grade 4 except for rash and (drug related) fever

Secondary outcome

Secondary end-points include the establishment of an immune response against

tumor asscoiated antigens and the model antigen KLH. Read-out parameters are

the side effects, immune responses, anti-tumor response and survival of this

DC-based immunotherapy* both in vivo and in vitro.

Study description

Background summary

Malignant mesothelioma is an aggressive malignant pleural disease, related to asbestos exposure. Due to the long time interval between exposure and disease and the abundant environmental presence of asbest, incidence is still rising. Prognosis is poor with a median survival of 12 months even with cytotoxic chemotherapy. At present cytotoxic chemotherapy is the only evidence based treatment for the disease, but efficacy is limited. No major improvements were made with so-called targeted agents in mesothelioma. Surgery may have a role in a limited number of patients, but recurrences do often occur. No curative treatment options are available.
We have shown both in a murine model, as for the first time in patients, that dendritic cell-based immunotherapy induces tumor specific T-cell responses. In two trials, 20 patients were treated with this autologuous vaccin. The dendritic cells were loaded with tumor material which was obtained from the patient before the start of chemotherapy. It was found to be a safe treatment. Apart from a flu like syndrome for 2 to 4 days in a minority of patients no side effects were detected. In the patients a tumor specific immune response was generated which was not present before the treatment. Survival rates in the patients were encouraging, with 4 patients still alive with a shortest follow up of 2 years.
However the quality and quantity of the autologuous tumor cell lysate to load the dendritic cells was a major impediment for this trial. In most patients the lysate is generated from pleural effusions. In others from pleural biopsies. Only in 20% of screened patients, these patient materials were of sufficient quality to generate the tumor lysate. As in mesothelioma no common tumor antigen is present it is not possible to load the dendritic cells using such an antigen. Apart from that, it is now becoming more and more evident that multipotent targeting of a tumor by the immune system may be more efficient then the single antigen targeting.
We have now developed a clinical grade allogeneous tumor cell lysate which can be used to load dendritic cells of patients. The allogeneous lysate is composed of a mixture of tumorantigens derived from 5 cellines obtained from 5 patients. The patients were selected based on the difference in their growth pattern to cover the whole scala of MM. These cellines are immortal and provide an off the shelf source of tumor antigens with constant quality and quantity. In a murine

model this way of loading of dendritic cells was equally effective to the autologuous treatment.

Study objective

The objective of the present trial is to investigate the safety of an allogenic tumor cell lysate loaded onto autologuous dendritic cells (AlloDen) in patients with malignant mesothelioma (MM). Heretoo we will perform a phase I study with a classical 3*3 design.
The aim of this phase I protocol is to study the toxicity and safety of AlloDen (DC-based immunotherapy) in MM patients. Secondary end-points include the establishment of an immune response against TAA and KLH and overal survival. Read-out parameters are the side effects, immune responses, anti-tumor response both in vivo and in vitro.
In case no major toxicity problems will occur, the dose found to be safe established with this trial will be taken into phase II.

Study design

In the phase I study, a 3x3 design will be applied and 3 different dose levels of AlloDen (10*106 cells, 25*106 cells and 50*106 cells). If no dose-limiting toxicity (DTL) is encountered among the first three evaluable patients treated at a particular dose level, the next dose level can be opened. In case there is one DLT among the first three patients at a certain dose level, then 3 other patients will be treated at this dose-level. If in these total 6 patients, no other DLTs are seen (so in total 1/6 patients with a DLT), the next dose level can be opened. If there are more than 2 DLTs in a particular dose level, this level is considered to exceed the maximum tolerated dose and the dose level one level lower will be considered as the recommended dose for further studies. This approach implies that in the phase I part at least three and maximum 18 patients are needed
A leukapheresis is performed of which the monocytes are used for differentiation to DCs using different cytokines. The procedure to grow DCs in vitro and pulse them with tumor lysate is performed according to our former DC-immunotherapy protocols that were approved by the ethics committee (as in our former protocol METC-2008-109, CCMO NL24050.000.08).
Pulsed autologous DCs (AlloDen) are re-injected every two weeks. Quality control tests will be performed before the cellular vaccine is released (see IMPD [version 6]). After the third injection with AlloDen, revaccinations to boost the immunsystem are given in a 3 monthly interval until unacceptable toxicity.

Intervention

Patients will be injected with autologuous dendritic cells which are generated from monocytes obtainend from the patient via leucapheresis.

Patients will be injected both intravenously and intradermal with their own dendritic cells. These cells have been loaded with an allogenic tumor cell lysate.

Study burden and risks

The impact of our study on the participants is relatively high. Normally patients should be followed up every 6 weeks with radiographic examinations. Most patients do suffer from a disease which is killing in short notice.
The riks of the interventions are limited and no standard treatment is prohbited due to our study as there is none. From our former trials we knwo that patients are highly motivated to participate.
Patients have to undergo a couple of standard procedures especially for this trial, like a cathether in a blood vessel. This is an invasive procedure but risks are limited,. This iv entrance is neccesary everytime, for the leucopheresis, for blood samples and for the injection of the dendritic cells.
A leucopheresis is a standard procedure and will be performed according to guidelines. There is a limited risk for transient trombocytopenia and leucopenia.
The administration of cells who have been loaded with materials not derived from the patient is a potential risk and that is the subject of the study. Because not the lysate itself is administered to the patients but only when it is processed by the cells of the patient we expect these risks to be small. The dendritic cells are equipped to digest foreign materials in their function as antigen presenting cell.

To determine the side effects a low dose will be given in first instance. In our formed trials no side effects were foudn with 50 million cells and we now start at 10 million. In case of side effects an immune response could occur against the patients one cells, which can then be treated with immunosuppressive drugs.

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

The study population consists of adult patients with malignant mesothelioma who have been or have not been treated with chemotherapy. Patients treated with chemotherapy must not experience progressive disease during chemotherapy. In selected cases with low disease burden as determined by the multidisciplinary tumor board of Erasmus MC Rotterdam, patients can be included after diagnosis before any treatment.

Exclusion criteria

patients with mesothelioma progressive after chemotherapy

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2014
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	27-05-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2017
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	EUCTR2014-000800-84-NL
CCMO	NL44330.000.14