Immunochemotherapy: Do platin-based chemotherapeutics enhance dendritic cell vaccine efficay in melanoma patients?

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

Summary

ID

NL-OMON36238

Source
ToetsingOnline

Brief title
DC immunochemotherapy

Condition

- Skin neoplasms malignant and unspecified

Synonym
malignant melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: KWF en Stichting Nijmeegs Offensief Tegen Kanker

Intervention

Keyword: chemotherapy, dendritic cells, melanoma

Outcome measures

Primary outcome

The primary objective of the study is to investigate the immunogenicity and feasibility of combined chemotherapy-DC vaccination.

Immunologically responding patients are defined as: T cells isolated from vaccine challenged sites (DTH) that can be expanded and: 1) express T cell receptors specific for the vaccine, 2) show effector functions measured by IFNg secretion or cytolytic activity against tumor antigen expressing target cells.

Immunologically non-responding patients are defined as: No T cells, or T cells isolated from vaccine challenged sites (DTH) that cannot be expanded, or T cells that can be expanded but do not recognize tumor antigens, or can recognize tumor antigens but do not display T effector functions i.e. lysis of tumor cell targets or release of IFNg.

Secondary outcome

The secondary objective is to investigate the toxicity and clinical responses upon DC immunochemotherapy. Toxicity will be assessed using the Clinical Toxicity Criteria NCI CTC version 3.0. Tumor evaluation will be performed at baseline and every 3 months until progression according to modified RECIST criteria [30].

Clinically responding stage IV patients are defined as: patients with an

objective complete or partial response, or disease stabilization for at least 4 months duration.

Clinically non-responding stage IV patients are defined as: patients with progressive disease or stabilization for less than 4 months. Progression-free an overall survival will be documented as best response. In stage III patients the disease free survival will be documented.

Furthermore, the effect of cisplatin on immune inhibitory molecules on peripheral blood and on tumor material will be investigated.

Study description

Background summary

Melanoma is a highly malignant melanocyte-derived tumor. For patients with resected high-risk primary melanoma and regional lymphnode metastases (stage III), no standard systemic adjuvant treatment is available. For patients with distant metastases (stage IV) also no standard systemic treatment is available that has a benefit in survival. We have explored immunotherapy and have now vaccinated well over 200 stage III and IV melanoma patients with monocyte-derived dendritic cell (DC) vaccines and proved that DC therapy is safe with minimal side effects. We observed that long lasting tumor specific T cell-mediated immunological responses in ±30% of the patients is clearly linked to highly significant (p= <0.001) increased progression free- as well as overall- survival. It has now become obvious that cancer cells create an immunosuppressive microenvironment paralyzing the effector arm of the immune system. Successfully activated tumor-specific T cells encounter a large amount of suppressive networks at the tumor site, such as suppression by regulatory T cells, inhibitory molecules expressed by tumor cells, and a cytokine milieu that skews the T cells into an ineffective Th2 type of response [1]. This demonstrates that cancer vaccines will only be effective if at the same time we succeed in reversing immunesuppression.
Cytotoxic chemotherapy and radiotherapy have long been viewed as strategies that directly impact the viability of the tumor cell, and that the immune system contributed little to their efficacy. The commonly held opinion was that chemotherapy and immunotherapy could not be combined because of the myelo-suppressive effect of most chemotherapeutic agents. However, it becomes increasingly obvious that chemotherapy also possess the capacity to trigger

tumor antigen release and danger signals in a manner that provokes engagement of innate and adaptive immunity that may be capitalized upon.
Small proof-of-concept clinical trials in cancer patients indicate that the efficacy of anti-cancer vaccines may indeed be enhanced by chemotherapy [2]. Also our own preliminary observations indicate that chemotherapeutic agents, in particular platinum compounds (cisplatin, carboplatin and oxaliplatin) are immunogenic and may contribute to reverse tumor cell induced immunosuppression/immune deviation.
We hypothesize that DC vaccination, when combined with other more conventional anti-tumor treatments such as chemotherapy, that eradicate large numbers of cancer cells, may allow the T cells to clear the remaining cancer cells and to provide immunological memory to prevent relapse.

Study objective

This is an exploratory study and the primary objective is the immunogenicity and feasibility of combined chemotherapy-DC vaccination. The secondary objectives are the toxicity and clinical efficacy. This study will provide important data on the immunological efficacy of DC immunochemotherapy.

Study design

This study is an open label randomized phase II study.

Intervention

Stage III and IV melanoma patients will be vaccinated three times biweekly with mature DC injected intradermally and intravenously loaded with mRNA encoding tumor-associated antigens gp100 and tyrosinase and pulsed with KLH as an immune control. In arm A, each DC vaccine will be preceded by cisplatin infusion (50 mg/m2, 1-2h before DC injection). We aim to include 54 evaluable patients, 32 stage IV patients and 22 stage III patients within 2 months after radical regional lymphnode dissection, who will be randomized 1:1 between arm A (chemo+DC) and arm B (DC).

Study burden and risks

Based on the experience with our cytokine/PGE2-matured DC we expect that the DC vaccine 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 not greater than CTC grade 1. In an ongoing trial, we investigated whether oxaliplatin chemotherapy can be combined with DC vaccination in high-risk stage II and III colon cancer patients. They received capecitabine and oxaliplatin chemotherapy (the current standard adjuvant treatment for colon cancer) combined with peptide-pulsed DC injections during the 1st and 2nd chemotherapy cycles. This treatment was well tolerated with no

serious toxicity.

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

For both stage III and IV melanoma
- histologically documented evidence of melanoma
- stage III or IV melanoma according to the 2001 AJCC criteria
- HLA-A2.1 phenotype is required
- melanoma expressing gp100 (compulsory) and tyrosinase (non-compulsory)
- WHO performance status 0-1 (Karnofsky 100-70%)
- life expectancy >3 months
- age 18-70 years
- no clinical signs or symptoms of CNS metastases

- WBC >3.0×109/l, lymphocytes >0.8×109/l, platelets >100×109/l,
serum crea-tinine <150 µmol/l, serum bilirubin <25 µmol/l
- normal serum LDH (*450 U/l)
- expected adequacy of follow-up
- no pregnant or lactating women
- written informed consent
For stage III melanoma
- interval since regional lymph node dissection is <2 months
For stage IV melanoma
- at least one unidimensional measurable target lesions according to RECIST, not previously irradiated, and limited tumor burden, according to the responsible physician

Exclusion criteria

- prior chemotherapy, immunotherapy or radiotherapy <4 weeks prior to planned vaccination or presence of treatment-related toxicity
- history of any second malignancy in the previous 5 years, with the exception of adequately treated basal cell carcinoma or carcinoma in situ of the cervix
serious active infections, HbsAg or HIV positive or autoimmune diseases or organ allografts
- concomitant use of immunosuppressive drugs
- known allergy to shell fish (since it contains KLH)
- rapidly progressive disease
- any serious clinical condition that may interfere with the safe administration of DC

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-02-2011

Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	Platosin
Generic name:	Cisplatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-09-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-12-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-01-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2012
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	EUCTR2010-020228-23-NL
CCMO	NL32381.000.10