Myeloid and plasmacytoid blood dendritic cells for immunotherapy of stage III melanoma patients

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This is an interventional study and the primary objective is the immunogenicity of combined pDC and myDC vaccination. The secondary objectives are the biodistribution, the safety, quality of life and overall survival.

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

Summary

ID

NL-OMON42306

Source
ToetsingOnline

Brief title
myDC/pDC in stage III melanoma patients

Condition

- Skin neoplasms malignant and unspecified

Synonym
malignant melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Tumor Immunologie
Source(s) of monetary or material Support: ZonMw,Miltenyi Biotec GmbH

Intervention

Keyword: blood-derived dendritic cells, imaging, immunotherapy, melanoma

Outcome measures

Primary outcome

The primary objective is the immunogenicity of single and combined pDC and mDC vaccination.

Immunogenicity is defined as the antitumor immune response induced in stage III melanoma patients. Therefore, immunomonitoring will be performed that includes:

1) Type I IFN gene expression in PBMC shortly after vaccination. The occurrence of the type I IFN response in patients will be compared.
2) Proliferative, effector cytokine- and humoral responses to keyhole limpet hemocyanin (KLH).The occurrence of the response will be compared.
3) Functional response and tetramer analysis of DTH-infiltrating T cells against tumor peptides. The occurrence of the response will be compared.

Secondary outcome

The biodistribution, safety, quality of life and overall survival are secondary objectives.

Biodistribution is:

(a) The migratory capacity of blood DC in vivo.

(b) The localization of injected blood DC in dissected lymph nodes.

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. We have explored immunotherapy and have now vaccinated well over 300 melanoma patients with monocyte-derived dendritic cell (moDC) vaccines and proved that DC therapy is safe with minimal side effects. We observed that long lasting tumor specific T cell-mediated immunological responses are clearly linked to increased progression free- as well as overall- survival.
To date, most clinical trials use monocyte-derived DC (moDC) for DC vaccination of cancer patients. We observed an increase in median survival in stage III melanoma patients vaccinated with moDC in an adjuvant setting as compared to carefully selected historical controls (64 vs 31 months, p=<0.02). However, moDC may not be the optimal source of DC for DC-based vaccination studies, due to extensive culture periods and compounds required to obtain mature moDC. Since they do not require extensive culture periods, peripheral blood-derived DC may be a good alternative. We recently completed a clinical trial in stage IV melanoma patients using pDC. The results on both immunological outcome as well as clinical outcome are promising. Additionally, the first patients are vaccinated with blood-derived myeloid DC. In these patients tumor-specific responses are observed as well. Taken together, we demonstrated that it is feasible to use blood-derived pDC and myDC and that these cells can be activated and loaded with peptides before injection into melanoma patients. Based on in vitro data and preclinical studies, we hypothesize that the combination of blood myDC and pDC may induce stronger anti-tumor immune responses. The aim of this study is to investigate the immunogenicity of combined pDC and myDC vaccination.

Study objective

This is an interventional study and the primary objective is the immunogenicity of combined pDC and myDC vaccination. The secondary objectives are the biodistribution, the safety, quality of life and overall survival.

Study design

This study is an interventional study.

Intervention

Stage lll melanoma patients will receive pDC (arm A, n=7), myDC (arm B, n=7) or combined pDC/myDC (arm C, n=7). Subsequent vaccinations will be performed

according to the protocol: 2 biweekly vaccinations of intranodal injections with pDc, myDC or the combination with pDC and myDC. After each vaccination we will examine peripheral blood for proliferative and humoral KLH immune responses. After the vaccinations, a DTH with peptide-loaded blood DC is performed from which biopsies are taken for T cell analysis. lf patients remain disease free, we will repeat this cycle with a 6 months interval up to a total of three cycles. lf a tumor recurrence occurs a biopsy will be taken for laboratory evaluation.

Study burden and risks

Based on the experience with the pDC and myDC vaccination separately, we expect that the combined DC vaccine will be well tolerated. Common and expected side effects of DC vaccination are usually mild and include flu-like symptoms, not greater than CTCAE grade 1. During the skin test, a small amount of vaccine is injected into the skin of the back, this may give a local reaction at the injection site: redness, swelling and itching. Patient material (blood, lymph nodes and skin and tumor biopsies) will be requested during the current study.

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

- stage III melanoma according to the 2009 AJCC criteria
- cytological or histological documented evidence of stage III melanoma
- WHO performance status 0-1 (Karnofsky 100-70) (Appendix 1)
- life expectancy *3 months
- age 18-75 years
- WBC >3.0×109/l, lymphocytes >0.8×109/l, platelets >100×109/l,
serum creatinine <150 µmol/l, serum bilirubin <25 µmol/l
- normal serum LDH (*250 U/l)
- expected adequacy of follow-up
- no pregnant or lactating women
- written informed consent

Exclusion criteria

- irresectable stage III melanoma or stage IV melanoma
- any concurrent adjuvant therapy
- 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, known HbsAg or HIV positive, or autoimmune diseases or organ allografts
- concomitant use of oral immunosuppressive drugs
- known allergy to shell fish (since it contains KLH)
- any serious clinical condition that may interfere with the safe administration of DC or apheresis

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):	09-10-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	16-06-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-11-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-07-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	24-08-2015
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2015
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	EUCTR2010-023757-11-NL
CCMO	NL49528.000.14