Longitudinal analysis of tumor-specific T-cel immunity in irresectable stage IIIc and stage IV melanoma patients

Published: 04-04-2011
Last updated: 27-04-2024

• To study the effect of treatment (e.g. anti-CTLA4, BRAF inhibition, TIL therapy) on the size and diversity of melanoma-specific T cell populations as measured by MHC tetramer technology and antigen-specific cytokine production. • To examine...

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

Summary

ID

NL-OMON36481

Source
ToetsingOnline

Brief title
Tumor-specific immunity in melanoma patients

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: immunity, melanoma, T-cel, tumor-specific

Outcome measures

Primary outcome

Immunologic monitoring

Secondary outcome

None.

Study description

Background summary

Melanoma-specific T cell immunity
There is now widespread evidence that tumor-specific T cell responses can contribute to the control of melanoma. As an example, treatment of patients with ipilimumab (an anti-CTLA4 antibody) has shown a survival benefit in patients with metastatic disease. Likewise, treatment of patients with metastatic melanoma with ex vivo expanded tumor-infiltrating lymphocytes has been shown to result in a high response rate in two different centers.
At the same time, little is known about the longitudinal development of melanoma-specific T cell immunity upon immunotherapeutic treatment. Does the breadth or strength of the therapy-induced T cell response predict clinical course? Does reactivity against certain tumor-associated antigens correlate with tumor regression or with treatment-induced autoimmune disease (e.g. vitiligo). Better knowledge on the development of melanoma-specific T cell responses both in peripheral blood and at the tumor site is likely to offer leads for early monitoring of treatment response and for the development of more targeted immunotherapies.
Furthermore, it has been postulated that also other therapeutic strategies that have been developed or are currently in development for melanoma, may potentially exert their effect in part through the induction of a melanoma-specific T cell response. As a specific example, the release of melanoma-associated antigens upon inhibition of BRAF may promote the induction of T cell responses against these antigens. At present, no data are available on the relationship between treatment of melanoma with these types of drugs and the development of tumor-specific T cell responses, either in peripheral blood or at the tumor site.

Study objective

• To study the effect of treatment (e.g. anti-CTLA4, BRAF inhibition, TIL therapy) on the size and diversity of melanoma-specific T cell populations as measured by MHC tetramer technology and antigen-specific cytokine production.

• To examine treatment induced alterations in the immune infiltrates present within biopsies.

Study design

In total 50-100 patients with proven stage irresectable IIIc or stage IV melanoma can be enrolled in this study.

All patients will be informed about this study consisting of two parts: 1) To allow peripheral blood sampling for longitudinal analysis of melanoma-reactive immune responses and 2) To allow tissue collection through tumor biopsies prior to and during treatment. Patients will be asked to sign for each part of the study a separate signature form.
After having signed the ICF, a peripheral blood sample (100 ml) will be drawn prior to and during treatment, and isolated peripheral blood mononuclear cells will be frozen immediately for research purposes. If a metastasis is easily accessible and the patient signed the informed consent for tumor biopsies, a tumor biopsy will be taken before treatment and during therapy.

Sampling of blood and tumor tissue during therapy will be partly dependent on the type of treatment. For patients treated with standard chemotherapy (DTIC or temozolomide), blood and tumor tissue sampling will be done after 2 courses (coinciding with response evaluation).
Blood sampling of patients treated with targeted agents (incl. BRAF/MEK/PI3K/c-KIT inhibitors) will be done after one course (3-4 weeks of treatment) and at the moment of response evaluation (blood and tumor tissue).
Blood and tumor tissue sampling of patients on immune activating agents (incl. anti-CTLA4, anti-PD-1, anti-PD-L1, anti-CD40 mAb etc.) will be done at 3 months after initiation of treatment (coinciding with response evaluation).

The idea behind these different time points for follow-up samplings is based on the mode of action of the drug and the knowledge or expectation of the time to response. Ipilimumab, an immunotherapy-based treatment, results in rather slow response, whereas the novel targeted agents such as PLX4032, a potent BRAF V600E inhibitor, sometimes can give clinical responses after a few days of treatment. In order not to miss the peak of the immune response, the time points need to be different for the various drugs.

Study burden and risks

With regard tot blood sampling low burden and risks: hematoma may occur.
With regard to biopsies: hematoma, bleeding and pain. However, only biopsies will be taken of easily accesible areas so the burden and risks will be minimalized.

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 or cytologically proven irresectable stage IIIc or IV melanoma
-Age above 18 years
-WHO performance score 0, 1 or 2 at the time of study entry
-Written informed consent

Exclusion criteria

-Severe anemia (Hb < 6.0 mmol/L)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-04-2011
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	04-04-2011
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL35235.058.11