Enhancing anti-melanoma activity of T-cells

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To test in vitro and in vivo therapeutic effects of new immunotherapeutic strategies in preclinical in vitro models and in mouse models on melanoma patient derived malignant cells.

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

Summary

ID

NL-OMON36999

Source
ToetsingOnline

Brief title
MIO, Melanoma Immunotherapy Optimization

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, T-cell transfer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF

Intervention

Keyword: immunotherapy, melanoma

Outcome measures

Primary outcome

The main study parameter in vitro is the percentage enhancement of the anti-melanoma activity of autologous T-cells armed with scFv:TRAIL. Enhanced anti-tumour activity of T-cells will be assessed in vitro by evaluating their capacity to induce apoptosis and loss of cell viability in autologous melanoma cells.

The main study parameter in vivo is the % increase in treatment efficacy determined in a mouse model xenografted with primary patient-derived melanoma cells and reconstituted with autologous patient-derived immune cells. Treatment efficacy will be assessed based on tumour outgrowth.

Secondary outcome

Additional in vitro parameters; T-cell proliferation (e.g. by CFSE fluorescent cell labelling), T-cell co-stimulation (e.g. by measurement of cytokine production), T-cell phenotype (e.g. by evaluation of TIM-3/PD-1 as markers for exhausted T-cells).
Additional in vivo parameters: the number of tumor-infiltrated lymphocytes, the phenotype of infiltrated lymphocytes (incl. exhausted T-cell phenotype).

Study description

Background summary

From tumor immunological research it has become apparent that certain subpopulations of T-lymphocytes of the patient can infiltrate a tumor. These so-called Tumor Infiltrating Lymphocytes (TILs) are apparently attracked by the tumor but also have substantial activity against these tumors. It appears that these TILs are not fully succesful in fully eliminating the tumorcells. Derived from recent research it became evident that patients with more TILs have a better prognosis compared to those with less. Many attempts have been made to use this concept of TILs in the clinic with variable succes, and in particular in melanoma patients. TILs are first isolated from a patients' tumor, activated outside the body and subsequently reinjected into the patient. Data from a recent clinical trial showed that this strategy is succesful in ~20% of patients with a more progressed stage of disease. Overall survival data revelead that complete responders, 3-7 year survival advantage could be reached. Nevertheless, 80% of patients with advanced disease do not respond to this strategy. The current project develops further the concept of adoptive T-cell transfer by increasing the efficacy of TILs. The approach is that T-cell can be loaded with an additional effector on their surface, which enhances the anti-tumor activity of such a pre-loaded T-cell. This effector is called TRAIL, a protein with a strong anti-tumoricidal effect, with minimal or no activity against healthy cells. By coupling a so-called antibody fragment to TRAIL, the T-cell can be drapped with a multitude of the conjugates to enhance its efficacy. In preliminary data, an enhancement of 500x can be reached by this approach in tumor killing.

Study objective

To test in vitro and in vivo therapeutic effects of new immunotherapeutic strategies in preclinical in vitro models and in mouse models on melanoma patient derived malignant cells.

Study design

In the current project the approach of enhancement of T-cell activity will be investigated. In patient derived material either from primary melanoma or metastasized melanoma, TILs will be islolated and enhanced and subsequently tested in vitro for their efficacy on different cell lines and the patients'melanoma cells. Furthermore, immunological cells (i.e. T-cells) derived from peripheral blood will be isolated and tested in combination with the tissue obtained from the same patient. for this so-called enhanced efficacy Additionally, tissue obtained from patients will be used in mouse models to test the anti-meloname adoptive T-cell ehanced therapy in vivo. This study will provide us with important information on the feasibility of the proposed approach for future clinical translation in patients. A total number of 112 samples will ne needed to analyse our primary end-point, with a total of 40 ml

of blood per patient.

Study burden and risks

During the surgical procedure, tumormaterial will be excised for histopathological examination. Part of the material, after primary use by the pathologist for the diagnostic process, will be used for in vitro analyses and testing of TILs on this material. Also 4 tubes of blood (40ml/patient) will be taken without a significant risk or burden on the patient, besides pain and hematoma on the puncture site for blood sampling

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1 BA11
Groningen 9700 RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1 BA11
Groningen 9700 RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

patients with primary and/or metastasized melanoma who need to undergo a surgical procedure

Exclusion criteria

no exclusion criteria;

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-04-2013
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	04-12-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-000507-33-NL
CCMO	NL40625.042.12