Detection of recirculating tumor-associated tissue macrophages and circulating melanoma cells as a tool for monitoring melanoma patients: a pilot study.

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Primary Objective: - Investigate whether recirculating tumor-associated tissue macrophages (TiMas), as well as circulating melanoma cells can be detected using high-end flow cytometry methods in peripheral blood from melanoma patients.Secondary…

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

Summary

ID

NL-OMON54197

Source
ToetsingOnline

Brief title
MelanoScan

Condition

- Skin neoplasms malignant and unspecified
- Skin neoplasms malignant and unspecified

Synonym
Melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Immunologie
Source(s) of monetary or material Support: European Research Council (ERC)

Intervention

Keyword: Melanoma, Monitoring, Tumor-associated macrophage

Outcome measures

Primary outcome

The number of TiMas containing melanocyte and/or melanoma-specific peptides in their phagolysosomes and circulating melanoma cells in peripheral blood, expressed as percentage per total circulating TiMas and as absolute count (cells/microliter).

Secondary outcome

- Identification of proteins present in melanocytes and melanoma cells and their possible post-digestion peptides.
- Proof of recirculation of tissue macrophages (containing post-digestion peptides) from the tissue of origin (skin/ epithelial layer) to peripheral blood via the lymph system.
- Investigate the presence of circulating melanoma cells and recirculating tissue macrophages (containing post-digestion peptides) in lymph nodes by flow cytometry and evaluate the possible support of this analysis in staging methodologies performed by the pathologist.
- Evaluate the *normal background* of melanoma/melanocyte peptide positive recirculating TiMas in healthy individuals and in patients with other (non-melanoma) skin diseases, such as inflammatory diseases.

Study description

Background summary

Every year, over 6,000 patients are diagnosed with cutaneous melanoma in The Netherlands. In the case of a stage IB or higher, a sentinel lymph node examination is performed to determine the stage of melanoma. After the initial diagnosis, periodic physical check-ups, and imaging in the case of suspected metastatic disease, are performed to detect disease progression and response to (adjuvant) treatment. These regular physical check ups are performed by a dermatologist or surgeon and include skin and lymph node station examination. In the case of (suspected) metastasized disease, the medical oncologist is involved. Visual skin examination is performed with the aid of dermoscopy (a handheld microscope), which can increase diagnostic accuracy, but still has a limited specificity, resulting in a high number of benign melanocytic lesions being unnecessarily excised. To lower this number, a new diagnostic tool is needed to help distinguish between benign moles and cutaneous melanoma, which should be fast, minimally invasive, and cost-effective. Such new tool would help to diagnose and monitor melanoma patients, and could assist in determining the best treatment for individual patients. Furthermore, there are specific groups of individuals who have a higher risk of developing melanoma in life, including people with hereditary melanoma due to mutations in the CDKN2A gene. In addition, patients with a history of multiple melanomas, or those with multiple atypical melanocytic nevi are at increased risk of melanoma development. These high-risk groups undergo regular periodic surveillance, consisting of once or twice yearly skin examination to investigate the skin for possible melanomas. These patients could benefit from a newly developed screening/diagnostic tool, which might assist the physician in examination of the skin and possible diagnosis of melanoma.
One possible approach to improve the screening, staging, and monitoring could be the detection of circulating tumor cells (CTCs) in peripheral blood. Some studies already showed that the presence of CTCs is related to relapse after treatment and treatment response. However, these CTCs usually have a low frequency, which implies substantial volumes of peripheral blood need to be analyzed. In general, the analysis of CTCs requires 8-10 mL of peripheral blood, in which 0-291 CTCs are detected, varying per CTC method and melanoma stage. Another possible approach involves the analysis of immune cells, which continuously perform sensitive intra-tissue scanning. In particular monocytes and tissue macrophages (TiMas) are interesting, since these cells phagocytize and digest apoptotic cells and tissue debris, including dying cancer cells. Recent evidence suggests that at least part of these TiMas can recirculate via lymph nodes to the bloodstream, where they might be detected and scanned for their phagolysosomal content. Supporting data for this recirculation concept has been obtained in glioma patients, where brain-specific proteins were identified in recirculating TiMas in peripheral blood. If this TiMa

recirculation concept is true, the tissues involved in this recirculation pathway, being primary tissue (e.g. skin), lymph node, and peripheral blood, should contain (recirculating) TiMas, containing tissue-specific and/or tumor-associated peptides in their phagolysosomes. This would imply that detection of recirculating TiMas and antibody-based scanning of these TiMas for the presence of tissue-specific and/or tumor-associated peptides has the potential to be a powerful tool for screening and monitoring of cancer patients. Considering that melanomas originate from melanocytes, the to-be-detected tissue-specific and/or tumor-associated peptides in melanoma patients should be melanocyte specific and/or melanoma-associated. Since melanocytes are most abundantly present in the skin, and to a much lesser extent in the retina, inner ear, the meninges and mucosal surfaces, detection of melanocyte-specific and/or melanoma-associated peptides in peripheral blood most likely indicates aberrant processes in the skin. Since melanocytes are a distinct cell type, melanocyte-specific proteins like GP100, MART 1, and tyrosinase could be suitable candidates to identify melanocyte-specific and/or melanoma-associated peptides.
In this study, we want to investigate the presence of possible recirculation of tumor-associated TiMas via lymph nodes to peripheral blood and circulating melanoma cells in melanoma patients, and evaluate the potential usefulness of flow cytometric detection of these TiMas and circulating melanoma cells in lymph nodes and peripheral blood of cutaneous melanoma patients to support screening for early diagnosis in high-risk groups, support diagnosis and staging of melanoma, and to monitor patients over time to assess treatment effectiveness and potential disease progression.

Study objective

Primary Objective:
- Investigate whether recirculating tumor-associated tissue macrophages (TiMas), as well as circulating melanoma cells can be detected using high-end flow cytometry methods in peripheral blood from melanoma patients.

Secondary Objective(s):
- Explore which proteins are present in melanoma cells and identify potential post-digestion peptides.
- Investigate whether recirculating tumor-associated tissue macrophages containing post-digestion peptides can be found in the recirculation pathway, being primary tissue (skin), lymph nodes, and peripheral blood, to proof recirculation of tissue macrophages.
- Investigate whether flow cytometric detection of recirculating tumor-associated tissue macrophages containing post-digestion peptides and circulating melanoma cells might assist in staging methodologies performed by the pathologist in involved lymph nodes.
- Investigate the *normal background* of melanoma/melanocyte peptide positive TiMas in blood samples of healthy individuals and patients with non-melanoma

skin diseases, such as inflammatory skin diseases.

Study design

This is a prospective cohort study performed in four phases, where Phase 1 is focused on the identification of melanoma/melanocyte-specific proteins and the corresponding post digestion peptides for development of the diagnostic tool; Phase 2 aims at evaluating the recirculation of macrophages from the tissue (skin) to the lymph nodes and peripheral blood using antibodies raised against the melanoma/melanocyte-specific protein fragments (as defined in Phase 1), and will be divided in Phase 2a, 2b and an optional 2c; Phase 3 will assess the *background levels* of the newly developed diagnostic tool in healthy subjects and patients with non-melanoma skin diseases.

Study burden and risks

Blood will be drawn via venipuncture in the arm. This can be an uncomfortable experience and can cause local pain of hematoma. Otherwise, no risks or interventions are part of this study. Since all visits are concurrent with diagnostic visits, participants will not lose much time participating in this study.

Contacts

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Selecteer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

General: • At least 18 years old • Able to understand the patient information • Diagnosed with, or a lesion high likelihood of, a cutaneous melanoma Phase 1: • Skin lesion with a diameter of >1 cm, highly likely of melanoma or loco-regional metastases, including local recurrences and in-transit metastasis or hematogenic or lymphogenic metastasis. Phase 2A: • Bulky lymph node disease who undergo debulking surgery. Phase 2B: • Hematogenic or lymphogenic metastasis who undergo debulking surgery. Phase 3: • Different control groups: lichen planus, psoriasis, dermatitis, vitiligo, atopic eczema, and individuals with >100 moles.

Exclusion criteria

• Immune disorders other than stated in the control groups
• Patients undergoing systemic cytotoxic or immunosuppressant therapy
• Uveal or mucosal melanoma
• Anamnestic pregnancy

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-01-2022
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	16-07-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	07-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	24-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	NL74845.058.20

Study results

Results posted:	05-02-2024
Actual enrolment:	2

First publication
05-02-2024