Randomized phase II study using a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 in metastatic melanoma

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A pilot feasibility study (n=5) will be performed to evaluate the feasibility (logistics, timing) and safety of administering autologous tumor infiltrating lymphocytes (TIL) generated at the NKI-AVL infused in conjunction with systemic high-dose...

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

Summary

ID

NL-OMON34085

Source
ToetsingOnline

Brief title
Lymphodepletion, TIL and interleukin 2

Condition

- Skin neoplasms malignant and unspecified

Synonym
malignant melanoma, skin cancer

Research involving

Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Giften;waaronder een onvoorwaardelijke eenmalige gift van Novartis.,Novartis

Intervention

Keyword: interleukin 2, lymphodepletion, melanoma, TIL treatment

Outcome measures

Primary outcome

Part I: Pilot study:

To examine whether the logistics and timing of this complex treatment can be managed properly without delays for the patients. If necessary, this will be optimized before entering the RCT. In addition, the toxicity according CTC and response rate according RECIST 1.1 will be documented.

Part II: Randomized controlled phase II study:

Primary endpoint: Increase in median progression free survival from 2 to 6 months

Secondary outcome

Part II: Randomized controlled phase II study:

Secondary endpoint: Objective response rate (RECIST), 1-year PFS, median overall survival, toxicity.

Study description

Background summary

The five-year survival of patients with metastatic melanoma is approximately 5%. Combination chemotherapy can induce objective regressions of melanoma but median response durations are short, and this treatment is rarely, if ever, curative. Approximately 15% of melanoma patients treated with high-dose interleukin-2 (Proleukin) experience objective regressions, with approximately a third of these responses being complete and durable. No other standard therapies are available for patients who do not respond to or relapse after chemotherapy or interleukin-2 (standard treatment in the USA).
Prior preclinical and clinical studies have shown that tumors from patients with advanced melanoma contain tumor-infiltrating lymphocytes (TIL) with anti-tumor reactivity targeting a variety of melanoma-associated antigens.
Prior clinical trials have shown that these TIL can be expanded in vitro using interleukin-2 with OKT-3 antibody stimulation and can cause regression of melanoma when adoptively transferred back to the patient.
Preclinical mouse models and clinical studies have shown that host immunosuppression prior to the adoptive transfer of tumor-reactive lymphocytes greatly enhances their anti-tumor effect.
Using a preparative non-myeloablative regimen of cyclophosphamide and fludarabine, a single institution phase II study in 43 patients showed a 51% objective response rate to TIL and interleukin-2, with complete and durable partial responses in a patient population that was heavily pretreated. Thus, in this trial we will investigate whether TIL treatment improves progression free survival in randomized phase II study compared to the current standard of care (dacarbazine chemotherapy). If PFS is indeed significantly broader application of this approach for patients with advanced melanoma should pursuit.

Study objective

A pilot feasibility study (n=5) will be performed to evaluate the feasibility (logistics, timing) and safety of administering autologous tumor infiltrating lymphocytes (TIL) generated at the NKI-AVL infused in conjunction with systemic high-dose interleukin-2 after non-myeloablative chemotherapy in patients with metastatic melanoma.
After this the randomized controlled phase II study will follow to evaluate whether this treatment can result in tripling the median PFS when randomly compared to *standard dacarbazine chemotherapy* in stage IV melanoma patients, to evaluate whether this treatment can cause consistent and durable objective responses in stage IV melanoma patients and a constructive technology assessment will be performed to evaluate the impact of the TIL treatment on patients and organizational processes.

Study design

Part I: Pilot study (5 patients)

Patients will undergo surgical resection of a melanoma metastasis of 3 cm (dm) to grow TIL in vitro. Once TIL have been generated from these cultures, cells will be rapidly expanded for adoptive transfer. Patients will undergo leukapheresis to obtain *feeder cells* for rapid expansion protocol.
Patients will receive a non-myeloablative lymphocyte-depleting preparative regimen consisting of cyclophosphamide (60 mg/kg/day X 2 days i.v.) and fludarabine (25 mg/m2/day IV X 5 days). Following this regimen, patients will receive an intravenous adoptive transfer of at least 5 x 10^9 TIL followed by high-dose intravenous interleukin-2 (Proleukin) (600.000 IU/kg/dose every 8 hours for up to 15 doses).
Supportive care consisting of blood or platelet transfusions is given until spontaneous hematopoietic recovery occurs. A complete assessment of evaluable lesions will be conducted 6 weeks after cell infusion and periodically after that to obtain best objective response by RECIST.
During this pilot study, special focus will be on logistics and timing: waiting time for metastasectomy, planning of leukapheresis, admission to the hospital for start of chemotherapy. Timing of TIL infusion and start of high-dose IL-2. Release from hospital.

Part II: Randomized controlled phase II study

Patients with metastatic (stage IV) melanoma, not previously treated systemically for stage IV disease will be randomized to either treatment arm A or treatment arm B.

Arm A: standard Dacarbazine chemotherapy (800 mg/m2 x 1 day i.v., q 3 weeks).
Arm B: fThe experimental TIL treatment. First the patients will undergo resection of one metastasis of 3 cm (dm). Once TIL can be grown from this tumor, the patient need to undergo leukapheresis to gain T-cells for the expansion of TIL. Before they are given the T cell infusion, the patients will be treated with non-myeloablative chemotherapy (cyclophosphamide 60 mg/kg/day x 2 days i.v., fludarabine 25 mg/m2/day x 5 days i.v.) followed by intravenous adoptive transfer of at least 5 x 10^9 TIL followed by high dose interleukin-2 (Proleukin) (600.000 IU/kg/dose every 8 hours for up to 15 doses).

Intervention

Pilot study:
Patients need to undergo surgery to obtain a metastasis of 3 cm (dm) that will be used to culture TIL. Only when these cells can be cultured in vitro, patients will be hospitalized for leukapheresis, non-myeloablative chemotherapy, and intravenous infusion of in vitro expanded TIL followed by high dose bolus interleukin-2 treatment.

Randomized phase II study:
Patients will be randomized for either standard treatment with dacarbazine or the experimental TIL treatment. Patients randomized for standard treatment will

receive dacarbazine 800 mg/m2 x 1 day i.v. q 3 weeks. Patients randomized for TIL treatment first need to undergo surgery to obtain a metastasis of 3 cm (dm) that will be used to culture TIL. When generation of TIL is successful, patients will undergo interventions as described above in Study design. The patients for whom no TIL can be generated, will be taken off study. They will be treated with dacarbazine according to the standard chemotherapy arm.

Study burden and risks

The TIL treatment will involve surgery of one melanoma metastase of 3 cm (dm), leukapheresis, in-hospital non-myeloablative chemotherapy, infusion of TIL, an intravenous high dose bolus IL-2 treatment and 2 biopsies will be taken after treatment. Although this treatment and toxicity has been demonstrated to be well manageable, common toxicities from non-myeloablative chemotherapy (transient bone marrow suppression requiring red cell and platelet support, increased chance of bacterial, viral and fungal infections, requiring antibiotics) and high dose IL-2 (high fever, rash, low blood pressure and decreased urinary output, edema requiring saline infusion support) may or will occur. Due to the infusion of TIL, patients may develop signs of melanoma associated autoimmune diseases such as vitiligo and uveitis. The latter, which is the more serious side effect, has been shown to respond promptly to topical corticosteroid treatment. However, the fact that these patients may have a high chance of durable objective responses, which otherwise would occur, justifies for the burden and possible toxicities.

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

• Patients must have metastatic melanoma with a resectable metastatic lesion of sufficient size (>= 3 cm) and must be willing to undergo such a resection for experimental purposes.
• Patients must be >= 18 years of age and must have measurable metastatic melanoma (in addition to the resected lesion).
• Patients must have a clinical performance status of ECOG 0 or 1.
• Patients of both genders must be willing to practice a highly effective method of birth control during treatment and for four months after receiving the preparative regimen.
• Patients must be able to understand and sign the Informed Consent document.
• Hematology: Absolute neutrophil count greater than 1.5 x 10^9/L without support of filgrastim.
Platelet count greater than 100 x 10^9/L.
Hemoglobin greater than 5 mmol/L.
• Chemistry
Serum ALAT/ASAT less than 3 times the upper limit of normal, unless patients have liver metastases (< 5 times ULN).
Serum creatinine clearance 50 ml/min or higher.
Total bilirubin less than or equal to 20 micromol/L, except in patients with Gilbert*s Syndrome who must have a total bilirubin less than 50 micromol/L.
• Serology:
Seronegative for HIV antibody.
Seronegative for hepatitis B antigen, and hepatitis C antibody.
Seronegative for lues.

Exclusion criteria

• Life expectancy of less than three months.
• Patients with metastatic ocular or mucosal melanoma.
• Requirement for systemic steroid therapy.
• Patients who have a history of more than two CNS metastases.
• Patients who have any CNS lesion that is symptomatic, greater than 1 cm in diameter or shows significant surrounding edema on MRI scan will not be eligible until they have been

treated and demonstrated no clinical or radiologic CNS progression for at least 2 months.
• Any immunosuppressive chemotherapy or systemic steroid therapy within the last 3 weeks.
• The following patients will be excluded because of inability to receive high dose interleukin-2:
History of coronary revascularization
Documented LVEF of less than 45% in patients with:
o Clinically significant atrial and/or ventricular arrhythmias including but not limited to: atrial fibrillation, ventricular tachycardia, 2° or 3° heart block
Documented FEV1 less than or equal to 60% predicted for patients with:
o A prolonged history of cigarette smoking (greater than 20 pack/year within the past 2 years)
o Symptoms of respiratory distress
• All patients* toxicities due to prior non-systemic treatment must have recovered to a grade 1 or less. Patients may have undergone minor surgical procedures or focal palliative radiotherapy (to non-target lesions) within the past 4 weeks.
• Women who are pregnant or breastfeeding.
• Any active systemic infections, coagulation disorders or other active major medical illnesses, such as active autoimmune disease requiring anti-TNF treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-05-2011
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	DTIC
Generic name:	dacarbazine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TIL treatment
Generic name:	tumor infiltrating lymphocytes

Ethics review

Approved WMO Date:	06-10-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-03-2013
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	EUCTR2010-021885-31-NL
CCMO	NL33250.000.10