Adoptive T cell therapy in patients with recurrent ovarian cancer

Published: 12-10-2017
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Primary: • Evaluate the safety of TIL, alone or with IFNα, in patients with recurrent platinum sensitive EOC during standard chemotherapy (carboplatin and paclitaxel).Secondary: • Evaluate signs of activity and underlying mechanisms (response rate,...

Ethical review	Approved WMO
Status	Completed
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46501

Source
ToetsingOnline

Brief title
OVACURE

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
cancer of the ovary, Epithelial Ovarian Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: OVACURE

Intervention

Keyword: chemotherapy, recurrent ovarian cancer, T cell therapy, TILs

Outcome measures

Primary outcome

- TIL (plus INFα) related toxicity according to NCI CTCAE v4.03

Secondary outcome

Signs of activity:

o Best overall response according to RECIST 1.1 and immune response criteria

(irRC).

o Disease control rate (DCR: CR+PR+SD) at 6 months.

o Progression free survival and overall survival.

o Analysis of underlying mechanisms by evaluation of hypothesis-related immune

parameters (including immune modulation by chemotherapy, TIL and IFNα and

functional capacity of TIL).

Study description

Background summary

The clinical outcome of standard treatment for patients with epithelial ovarian cancer (EOC) is poor, with a 5-year survival rate of only 35%. Ovarian cancer is a highly immunogenic tumor and good survival is tightly linked to the presence of tumor-infiltrating CD8+ T cells and the absence of immunosuppressive immune cells [Zhang et al, NEJM, 2003, Hwang,WT Gynecol Oncol 2012]. The clear correlation between T cell infiltration and disease progression suggests that EOC may be sensitive to adoptive cell therapy by infusion of ex-vivo expanded autologous Tumor Infiltrating Lymphocytes (TIL), provided that immune suppression is reduced. Carboplatin+paclitaxel chemotherapy is directly killing tumor cells, but was also shown to alleviate immunosuppression for 2 weeks coinciding with enhanced T-cell immunity, potentially creating a window of opportunity for T-cell based immunotherapy. In

addition, there is evidence that interferon alpha (IFNα) may not only work as a low toxic preconditioning regimen that creates the space required for the infused TIL, but that it also supports the TIL by sustaining their persistence and indirectly their function via upregulation of HLA class I on tumor cells and by decreasing the number of regulatory T cells.
Based on this we hypothesize that a synergistic clinical effect may be obtained when TIL are administered during treatment with chemotherapy that might even be increased when IFNα is added to the TIL infusion and chemotherapy.
We therefore propose to study the feasibility and safety of TIL administration in the window of opportunity created by carboplatin-paclitaxel chemotherapy with or without supportive IFNα. Furthermore, we will perform exploratory studies to analyze and confirm the proposed underlying mechanisms.
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Study objective

Primary:
• Evaluate the safety of TIL, alone or with IFNα, in patients with recurrent platinum sensitive EOC during standard chemotherapy (carboplatin and paclitaxel).

Secondary:
• Evaluate signs of activity and underlying mechanisms (response rate, disease control rate, progression free and overall survival, immune modulation by chemotherapy and by IFNα, TIL and IFNα, as well as T-cell reactivity).

Study design

A prospective, single center, open label, phase I/II study.

Intervention

Cohort 1 (n=3-6): Add TIL to standard chemotherapy (carboplatin+paclitaxel). TIL will be administered 2 weeks after the 2nd, 3rd and 4th chemotherapy cycle

Cohort 2: (n=3-6) Add TIL plus IFNα to standard chemotherapy (carboplatin and paclitaxel).
TIL will be administered 2 weeks after the 2nd, 3rd and 4th chemotherapy cycle and IFNα will be administered for 12 weeks during the TIL therapy.

Study burden and risks

The risk of participation are toxicity of the TIL, with or without IFNα, when added to standard chemotherapy.
For most patients, tissue will be obtained at primary surgery, while for some patients an extra biopsy will be necessary.

An extra biopsy is painful but rarely gives a bleeding or infection.

Patients will have to come to the hospital for the TIL infusions and have to be hospitalized for 24 h during the first TIL infusion.

Benefit:
Patients with recurrent ovarian cancer, have a poor prognosis for which further improvement of alternative treatment
options is necessary. The study offers a chance to obtain clinical benefit in these patients, that otherwise have a very bad prognosis.

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

• Age >= 18 years.
• OVACURE: Histologically proven epithelial ovarian cancer (EOC). Pre-OVACURE: Patients with stage IIIc or IV EOC that are treated with first line surgery can participate in the pre-OVACURE for TIL preservation out of the surgical specimen. In case of recurrent disease these TILs can be used.
• Recurrent ovarian cancer
• Presence of measurable progressive disease according to RECIST version 1.1 or elevated CA125>2 times the upper normal limit (UNL) within 3 months and confirmed.
• Expected survival of at least 3 months.
• WHO performance status 0-2.
• Within the last 2 weeks prior to study day 0, vital laboratory parameters should be within normal range, except for the following laboratory parameters, which should be within the ranges specified:
Hemoglobin >= 6,0 mmol/l
Granulocytes >= 1,500/µl
Lymphocytes >= 700/µl
Platelets >= 100,000/µl
Creatinine clearance >= 50 min/ml
Serum bilirubin <= 40 *mol/l
ASAT and ALAT <= 5 x the normal upper limit
LDH <= 2 x the normal upper limit
• Viral tests:
o Negative for HIV type 1/2, HTLV and TPHA
o No HBV (hepatitis B virus) antigen or antibodies against HBc in the serum
o No antibodies against HCV (hepatitis C virus) in the serum
• Able and willing to give valid written informed consent.
• Prior treatment, including immunotherapy e.g. with anti-PD(L)1, is allowed but systemic therapy and radiotherapy must have been discontinued for at least two weeks before study entry.
• Patients should have disease progression.

Exclusion criteria

• Patients with brain metastases.
• Clinically significant heart disease (NYHA Class III or IV).
• Other serious acute or chronic illnesses, e.g. active infections requiring antibiotics, bleeding disorders, or other conditions requiring concurrent medications not allowed during this study.
• Active immunodeficiency disease or autoimmune disease requiring immune suppressive drugs. Vitiligo is not an exclusion criterion.
• Other malignancy within 2 years prior to entry into the study, except for treated non-melanoma skin cancer and premalignant diseasein.
• Mental impairment that may compromise the ability to give informed consent and comply

with the requirements of the study.
• Lack of availability for follow-up assessments.
• Pregnancy or breastfeeding

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-11-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Roferon A
Generic name:	Interferon alpha-2a
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-10-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-02-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-03-2019
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	EUCTR2016-002404-25-NL
CCMO	NL63434.000.17