OVACURE - Adoptive T cell therapy in recurrent ovarian cancer

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Objectives: 1. The primary objective is to evaluate the safety and immune modulation of TIL plus IFN* in epithelial ovarian cancer (EOC) patients and to determine the optimal dose of IFN* that can be given in combination with chemotherapy.2....

Ethical review	Not approved
Status	Will not start
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46179

Source
ToetsingOnline

Brief title
OVACURE

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
Epithelial Ovarian Cancer

Research involving
Human

Sponsors and support

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

Intervention

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

Outcome measures

Primary outcome

The primary endpoint of this phase I clinical trial is to evaluate the safety and toxicity of Adoptive T cell therapy in combination with IFN* according to CTCAE version 4.0 criteria.

For platinum sensitive patients this will be studied in combination with chemotherapy and three cohorts of a reduced dose of IFN*.

For these 3 cohorts a phase I design will be followed: If a dose-limiting toxicity (DLT) occurs in one of the three patients

within one cohort, then three additional patients will be treated at that dose level. If a DLT occurs in 2/3 or 2/6 patients, the previous dose level will be expanded to at least 6 patients.

DLT is defined as follows:

Any DLT must be a toxicity that is considered related to study drug.

Hematologic

* Absolute neutrophil count (ANC) < 0.5 x 109/L for at least 7 days

* Febrile Neutropenia (ANC < 1.0 x 109/L, fever > 38.5oC)

* Platelets < 25 x 109/L

* Bleeding felt to be due to thrombocytopenia

Non-Hematologic:

* Diarrhoea > Grade 3 despite optimal loperamide use persisting * 2 weeks

* Nausea / vomiting > grade 3 despite optimal use of anti-emetics, persisting *

2 weeks.

* Other grade 3 / 4 effects thought to be treatment related

Secondary outcome

Secondary endpoints are the evaluation of a clinical response according to

RECIST 1.1 and immune response criteria (irRC), progression free survival (PFS)

and overall survival (OS). Clinical benefit is defined as Stable Disease (SD),

Partial Response (PR), or Complete response (CR). Additional endpoints are

blood CA125 levels and analysis of (induced) immune parameters in patient*s

blood and serum, in the T cells used for infusion and in the primary tumor.

Study description

Background summary

The 5 year survival of patients with epithelial ovarian cancer (EOC), despite standard therapy with surgery and if indicated perioperative chemotherapy, is 35%. There is an urgent need for an improved therapy.
The successful use of adoptive T-cell therapy (ACT) in melanoma and the clear correlation between T cell infiltration and disease progression in EOC suggests that EOC may display a similar sensitivity to TIL treatment. In order to be effective, transferred TIL should survive and persist in vivo, migrate to the tumor and eradicate tumor cells. To obtain TIL persistence and increase TIL survival after transfer we combine TIL infusions with low dose IFN-alpha (IFN*). We previously showed that this combination resulted in clinical benefit in 50% of the melanoma patients treated with ACT using PBMC-derived tumor-specific T cells [Verdegaal et al Canc.Immunol. Immunoth. 2011]. Recently, clinical benefit was also obtained in patients treated with tumor-derived TIL plus IFN* [unpublished data]. Once migrated to the tumor, the anti-tumor activity of T cells is dramatically affected by the presence of myeloid-derived suppressor cells (MDSC) in the tumor-microenvironment. From our clinical trials in patients with recurrent cervical cancer we know that the frequency of circulating myeloid cells (macrophages and MDSC) is increased in these patients, but that the myeloid cell compartment is normalized to levels observed in healthy subjects, after carboplatin+paclitaxel chemotherapy. We

also observed this normalisation circulating myeloid cells after chemotherapy in patients with recurrent ovarian cancer treated with gemcitabine. Notably, we showed that chemotherapy could be excellently combined with immunotherapy. The myeloid cell population is also altered in patients with ovarian cancer. As the patients in the current trial are also treated with carboplatin+paclitaxel or gemcitabine, a chemotherapy-driven normalization of the myeloid cell population and hence a better response to immunotherapy is expected. We therefore suggest to study whether clinical benefit can be obtained in ovarian cancer patients with a combination of TIL + low dose IFN* and chemotherapy.

Study objective

Objectives:
1. The primary objective is to evaluate the safety and immune modulation of TIL plus IFN* in epithelial ovarian cancer (EOC) patients and to determine the optimal dose of IFN* that can be given in combination with chemotherapy.
2. Secondary objectives:
a. Evaluation of the clinical response (according to RECIST 1.1 criteria) and immune response criteria (irRC), progression free survival (PFS) and overall survival (OS).
b. Immunological parameters will be evaluated and correlated to clinical response parameters.

Study design

This phase I clinical trial is a controlled intervention study. The safety, toxicity, clinical and immunological response will be evaluated.

Intervention

TIL for treatment will be cultured from tumor material obtained from primary surgery, as well as from biopsies . The latter reflect the way tumor material will be acquired from stage IIb-IIIb patients and for stage IIIc and IV tumor material will be obtained at primary surgery.

Patients with platinum sensitive tumor recurrence (n=6-18):
Patients will be treated with TIL infusions + IFN* in combination with chemotherapy. TIL therapy will be similar as described above.
Since we do not know whether the standard dose of IFN* that was used during ACT treatment of melanoma patients is tolerated when patients receive concomitant chemotherapy, we will study the combined TIL plus chemotherapy treatment in three cohorts using a reduced dose of IFN* (3x10e6 U every other day, n=3), the standard dose of IFN* (3x10e6 U daily, n=3) or pegylated- IFN* (PEG-Intron, 0,5 *g/kg (maximum dose 50 *g) once a week, n=3).

Patients with platinum resistant disease (n=6):

will be treated with TIL infusions + the standard dose of IFN* (3x10e6 U daily) combined with standard chemotherapy, gemcitabine.

Study burden and risks

Risk:
The risk of participation are toxicity of the ACT plus IFN*. For most patients tissue will be obtained at primary surgery and for some patients an extra biopsy will be necessary. An extra biopsy is painfull but rarely gives a bleeding or infection.

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

* Age * 18 years.
* Histologically proven epithelial ovarian cancer.
* 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 :
Lab Parameter Range
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 PD.

Exclusion criteria

Patients will be excluded from the study for any of the following reasons:
* 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 in situ cervical carcinoma.
* 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:	Will not start
Enrollment:	24
Type:	Anticipated

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:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Roferon A
Generic name:	Interferon alpha-2
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:	08-11-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	19-05-2017
Application type:	First submission
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

Register	ID
CCMO	NL56136.000.16