An exploratory study: Dendritic cells for immunotherapy of metastatic endometrial cancer patients

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

Summary

ID

NL-OMON47953

Source
ToetsingOnline

Brief title
DC for endometrial cancer patients

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
endometrial cancer

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Stichting Phillis

Intervention

Keyword: dendritic cells, endometrium cancer

Outcome measures

Primary outcome

The primary endpoint of the study is to evaluate the immune responses towards tumor peptide-loaded nDC in mEC patients. We will study: a) functional responses and tetramer analysis of DTH infiltrating lymphocytes against tumor peptides and b) type I IFN gene expression in PBMC shortly after vaccination, and c) proliferative, effector cytokine- and humoral responses.

Secondary outcome

The secondary objectives are the safety, feasibility and quality of life of nDC vaccinations.

Study description

Background summary

Dendritic cell vaccination
Prevention of infectious diseases through immunization is one of the greatest achievements of modern medicine. Nonetheless, considerable challenges remain for improving the efficacy of existing vaccines for therapeutic immunizations for diseases such as cancer. We were amongst the first groups worldwide that introduced tumor antigen-loaded dendritic cell (DC)-based vaccines in the clinic1-3. Effective immune responses and favorable clinical outcomes have indeed been observed4-7. Thus far, mainly conventional in vitro generated monocyte-derived DCs (moDC) have been used in clinical trials worldwide. In the past 14 years we have treated more than 375 patients and proven that DC therapy is feasible and non-toxic. We observed that long lasting tumor specific T cell-mediated immunological responses are clearly linked to increased progression free survival as well as overall survival8.
However, moDC may not be the optimal source of DCs for DC vaccination studies, due to extensive culture periods and compounds required to obtain mature moDC. Peripheral blood-derived DC (plasmacytoid dendritic cells (pDC) and myeloid

dendritic cells (myDC)) are possibly a better alternative since they do not require extensive culture periods. We recently completed a clinical trial in stage IV melanoma patients using plasmacytoid pDC. The results on both immunological outcome as well as clinical outcome are promising. These freshly isolated natural pDC prolonged median overall survival to 22 months in comparison to 7.6 months in matched historical melanoma patients who had received standard chemotherapy9. In patients receiving moDC-vaccinations, we did not observe such a clear increase in overall survival, suggesting that pDC-vaccines may induce even more potent anti-tumor responses than moDC-vaccines. In terms of immunological outcome transcription of both interferon-alpha (IFN-*) and interferon-beta (IFN-*) genes was clearly induced 4 hours after vaccination and decreased 20 hours later. An IFN gene signature is known to be highly important for eradication of viruses. This signature is indicative for a temporal systemic induction of type I IFNs. Type I IFN might also stimulate myDC and enhance their ability to cross-prime CD8+ T cells, thereby inducing more efficient anti-tumor T cell responses when compared with in vitro generated DC. This is supported by studies in mice: type I IFN were critical for the induction of anti-tumor immune responses10,11. In the 14 stage IV melanoma patients included in our myDC trial we observed already in 3 patients highly functional tumour-specific T-cells in peripheral blood and in DTH sites coinciding with tumour regression12. For comparison: in our trials with monocyte-derived DC, less bonafide T cell responses were seen after DC vaccination, suggesting that blood myDC induce more potent immune responses compared to monocyte-derived DC.
In conclusion, based on all these observations we are convinced that pDC and myDC employ different, and probably more optimal mechanisms to combat cancer. In addition, based on in vitro data and preclinical studies that suggest that blood pDC and myDC act synergistically, we hypothesize that the combination of myDC and pDC may induce stronger anti-tumor immune responses as compared to pDC or myDC alone, or moDC.

Immunotherapy in endometrial cancer
Endometrial cancer is the only gynaecologic malignancy with a rising incidence and mortality. While cure is routinely achieved with surgery alone or in combination with adjuvant pelvic radiotherapy when disease is confined to the uterus, patients with metastatic or recurrent disease exhibit limited response rates to cytotoxic chemotherapy, targeted agents, or hormonal therapy. Some figures: at the time of diagnosis, 67% of women have disease confined to the uterus and an associated 5-year survival rate of 95%. In contrast, the 8% of patients with distant metastases at the time of diagnosis have a 5-year survival rate of 17% and face the prospect of cytotoxic chemotherapy (primarily with taxanes, platinum and anthracyclines).
Given the unmet clinical need in this patient population, exploration of novel therapeutic approaches is warranted, and attention is turning to immunomodulation. Existing evidence suggests that endometrial cancer is sufficiently immunogenic to be a reasonable candidate for immunotherapy.

Dendritic cell vaccination after chemotherapy
Tumors exploit several mechanisms to suppress anti-tumor immune responses, including the recruitment of suppressive cells, such as myeloid-derived suppressor cells (MDSCs), into the tumor microenvironment13. The presence of MDSCs in the suppressive tumor microenvironment is correlated with decreased efficacy of several immunotherapies, including DC vaccination and ipilimumab14,15. Data obtained in our lab indicates that MDSCs can be targeted with platinum-based chemotherapeutics. In head-and-neck squamous cell carcinoma patients treated with six weekly dosages of cisplatin, the frequency as well as suppressive capacity of MDSCs were significantly inhibited two weeks after the last dose. Treating the patients with DC vaccination after six cycles of chemotherapy with carboplatin, might therefore have a positive impact on the clinical outcome of DC vaccination.

Antigen loading of dendritic cells
To be effective as an antigen-presenting cell, the MHC molecules of a DC must be loaded with antigenic cargo. In this study, DC will be loaded with well-defined common tumor antigens in the form of long peptides of two tumor associated antigens frequently shared by endometrial cancer, survivin and MUC1.

Study objective

The primary objective of this exploratory study is to show immunologic efficacy of tumor-peptide and tumor lysate-loaded natural DC in mEC patients undergoing chemotherapy. The immune-monitoring will include: a) functional response and dextramer analysis of DTH infiltrating lymphocytes against tumor peptides, b) type I IFN gene expression in PBMC shortly after vaccination, and c) proliferative, effector cytokine- and humoral responses to keyhole limpet hemocyanin (KLH), an immunogenic protein providing T cell help.

The secondary objectives are the safety, feasibility and quality of life of natural DC vaccinations in combination with chemotherapy.

Study design

This study is a single arm exploratory, single-centre study.

Intervention

Our study population consists of 8 mEC patients who receive chemotherapy with carboplatin and paclitaxel in a weekly schedule on week 1, 2, 3 and week 5, 6 and 717. In week 8, myeloid and plasmacytoid DC (nDC) loaded with tumor lysate and survivin and NY-ESO PepTivators will be injected intranodally. In all patients, extensive immunomonitoring will be performed. Patients who demonstrate stable disease, partial response or complete response continue with extended three-weekly chemotherapy17 with intranodal injection of nDC in week

17, 20 and 23.

Study burden and risks

Based on the experience with nDC inoculations in melanoma patients, we expect that the nDC will be well tolerated by mEC patients. More common and expected side effects of nDC vaccination are usually mild and include flu-like symptoms and local reaction at injection site, both not greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1. The side effects are completely reversible within 24-48 hours. Because of this the risk classification in relation to the chance of adverse events and the severity of the expected adverse events is defined as being negligible.
Weekly carboplatin paclitaxel is an effective used schedule in endometrial cancer17. Side effects of weekly carboplatin paclitaxel are bone marrow toxicity, with resulting granulocytopenia, decreased platelets and anaemia, nausea, vomiting, diarrhea and constipation and neuropathy.

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

* women * 18 years old with histologically confirmed stage IV or metastatic carcinoma of the endometrium of the endometroid, serous or carcinosarcoma type.
* Hormone receptor negative or
o resistant to hormonal therapy
o ineligible for hormonal therapy because of other reasons
* eligible for treatment with carboplatin paclitaxel combination chemotherapy
* Life expectancy * 6 months
* WHO/ECOG performance status 0-1 (Karnofsky index 100-70)
* WBC >2.0*109/l, neutrophils >1.5*109/L lymphocytes >0.8*109/L, platelets >100*109/L, hemoglobin >5,6 mmol/L (9.0 g/dL), serum creatinine <150 µmol/L, AST/ALT <3 x ULN, serum bilirubin <1.5 x ULN (exception: Gilbert*s syndrome is permitted)
* Expression of survivin and/or muc1 on tumor material
* Expected adequacy of follow-up
* Postmenopausal or evidence of non-childbearing status or for women of childbearing potential: negative urine or serum pregnancy test, within 28 days of study treatment and confirmed prior to treatment on day 1
* Written informed consent

Exclusion criteria

* Eligible for hormonal therapy
Uncontrolled hypercalcemia
* History of any second malignancy in the previous 5 years, with the exception of adequately treated basal cell carcinoma
* Known allergy to shell fish
* Heart failure (NYHA class III/IV)
* Serious active infections
* Active hepatitis B, C or HIV infection
* Active syphilis infection
* Autoimmune diseases (exception: vitiligo is permitted)
* Organ allografts
* An uncontrolled co-morbidity, e.g. psychiatric or social conditions interfering which participation
* Concurrent use of systemic corticosteroids > 10 mg daily prednisone equivalent
* Any serious clinical condition that may interfere with the safe administration of DC vaccinations
* Unable to undergo a tumor biopsy

* Pregnancy or insufficient anti-conception if reproduction is still possible

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-04-2019
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	01-04-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-04-2019
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	EUCTR2018-004467-31-NL
CCMO	NL68332.000.18

Study results

Date completed:	01-03-2021
Actual enrolment:	8