Isolation and immune profiling of human B lymphocytes for the development of potential diagnostic and therapeutic antibodies

Published: 25-05-2020
Last updated: 04-07-2024

We aim to study B cells derived from tumor and peripheral blood of uterine cancer patients in order to evaluate B cell-produced (tumor binding) antibodies for potential diagnostic and therapeutic interventions.

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

Summary

ID

NL-OMON55081

Source
ToetsingOnline

Brief title
AMELIA

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
endometrial cancer, Uterine cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Genmab,Genmab

Intervention

Keyword: B lymphocytes, Deficient mismatch repair (dMMR), DNA polymerase epsilon exonuclease domain mutation (POLE-EDM), Uterine cancer

Outcome measures

Primary outcome

The primary objective is to characterize B cell immune responses in uterine

cancer patients.

This pilot study is considered successful when;

• in 20% of the patients tumor binding antibodies are found (using B cells

derived from peripheral blood)

• in 20% of the patients tumor binding antibodies are found (using B cells

derived from tertiary lymphoid structures, if present)

Isolated B cells (intratumoral or peripheral blood) will be analyzed using e.g.

flow cytometry, immunochemistry, DNA/RNA sequencing and antibody production.

Tumor binding antibodies are defined as binding of the antibody to at least 2

endometrial carcinoma cell lines, which will be used as surrogate tumor model.

Secondary outcome

-

Study description

Background summary

Uterine cancer (UC) is the most common gynecological malignancy in the Western

world. Standard treatment comprises surgery with or without (chemo)radiotherapy. Despite an overall favorable prognosis, many women relapse and succumb to the disease.
Approximately 30% of all uterine cancers are characterized by a high mutational load resulting from: microsatellite instability (MSI-H), MisMatch Repair deficiency (dMMR) or mutations in the exonuclease (proofreading) domain of DNA polymerase epsilon (POLE-EDM).
MSI-H/dMMR and POLE-EDM occur in 20% and 12% of all uterine cancers (UCs), respectively. These tumors are characterized by a high number of mutation-associated neo-antigens (MANAs) and are therefore prime targets for immunotherapy.
Evaluation of MANA-specific responses during clinical immunotherapy has focused predominantly on CD8, and to a lesser extent CD4, T cell responses. However, recent work has also identified a key role for B lymphocytes in immunotherapy. In particular, MANA-rich tumors are characterized by extensive B cell infiltration and so-called tertiary lymphoid structures (TLSs), de novo lymphoid tissue associated with favorable prognosis and responses to immune checkpoint inhibitors. The migration of circulating B cells to peripheral organs has also been linked to potential immunotherapy-associated autoimmune-related side-effects.
Based on our earlier work, we hypothesize that MANA-specific T cells recruit B cells to tumors via release of the chemokine CXCL13. Infiltrating B cells could subsequently contribute to antitumor responses through several mechanisms, most notably through the formation of TLSs, production of anti-tumor antibodies, and as potent antigen-presenting cells (APCs). Here, we propose a first step towards addressing this hypothesis by analyzing de novo B cell antibody responses towards endometrial cancer

Study objective

We aim to study B cells derived from tumor and peripheral blood of uterine cancer patients in order to evaluate B cell-produced (tumor binding) antibodies for potential diagnostic and therapeutic interventions.

Study design

Prior to surgery (hysterectomy) PBMC*s (100mL) will be obtained. Tumor tissue removed during surgery will be evaluated by pathological examination according to standard-of-care procedures. The remaining *waste*-tumour tissue will be used for study procedures. DMMR testing will be performed according to standard-of-care by the pathologist. Additionally, tumor tissue sections from the same block will be used for DNA isolation (POLE-EDM testing) and immunohistochemical staining for at least CD3/CD20, CD4/CD8 and CD38/CD138 to identify tertiary lymphoid structures and antibody-producing plasma cells.
Since a hysterectomy is performed as standard of care procedure, RNA and single intratumoral B cells can be isolated and analyzed. B cells from different types

of uterine cancer (dMMR, POLE-EDM, TP53 mutant and NSMP) will be compared. PBMC*s collected prior to surgery and during follow up (optional) are used to assess the systemic B-cell responses. Single B-cells isolated from the surgical specimen will be used for single cell B cell receptor (BCR) sequencing and for antibody-screening. Whether patients will be approached for a second blood sample to confirm findings of interest will depend on the primary results

Study burden and risks

Participants will be asked to donate one blood sample during their normal diagnostic and therapeutic work-up. Some patients will be approached for a second sample. The first sample will be obtained prior to standard-of-care surgery (100 ml). Patients will be approached for a second blood sample to validate notable findings.

Risk of participation is considered minimal as an ordinary venapunction will be performed. Patients will not benefit from participation in the study.
This is a pilot study, if any potential diagnostic of therapeutic interventions are found, further options can be explored in a large-scale research project to contribute to the development of immunotherapy for uterine cancer.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed primary diagnosis of uterine cancer who are intended to be treated with hysterectomy will be enrolled in this study.
• The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

Exclusion criteria

• History of an autoimmune disease, specifically hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), or any other systemic intercurrent disease or condition that might affect the immunocompetence of the patient, or treatment with systemic highly immunosuppressive therapy (e.g. transplant recipients or patients who underwent a splenectomy)
• Use of systemic continuous corticosteroid therapy (e.g. prednisone i.v. or p.o. >7.5 mg / day).
• History of a second malignancy except for curatively treated low-stage tumors with a histology that can be differentiated from UC.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-10-2021
Enrollment:	67
Type:	Actual

Ethics review

Approved WMO Date:	25-05-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL73482.042.20