[18F]fluoro-PEG-folate PET/CT imaging in patients with epithelial ovarian cancer

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Primary objective:1. To evaluate the safety and tolerability of the [18F]fluoro-PEG-folate PET tracer2. To determine the pharmacokinetics (protein binding, biodistribution, clearance rate) of the [18F]fluoro-PEG-folate PET tracerSecondary objectives...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ovarian and fallopian tube disorders
Study type	Interventional

Summary

ID

NL-OMON52813

Source
ToetsingOnline

Brief title
[18F]fluoro-PEG-folate PET/CT imaging in epithelial ovarian cancer

Condition

- Ovarian and fallopian tube disorders

Synonym
Epithelial ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Bontius Stichting (vermogensfondsen)

Intervention

Keyword: Epithelial ovarian cancer, PET/CT, Preoperative assessment of tumor extent, Tumor-targeted molecular imaging

Outcome measures

Primary outcome

The primary objective of the study will be to evaluate the safety, tolerability and pharmacokinetics of the [18F]fluoro-PEG-folate tracer.

Tolerability assessments (blood pressure (mmHg), pulse rate (bpm), peripheral oxygen saturation, respiratory rate, temperature will be recorded at regular intervals (every 15 minutes) starting directly before administration and continued up to two hours after dosing. Following the [18F]fluoro-PEG-folate PET/CT scan, an ECG (PR, QRS, QT) will be performed. Additionally, (serious) adverse events and the concomitant use of other medications throughout the study period (defined as up to six weeks after the administration of the [18F]fluoro-PEG-folate tracer) will be recorded.

Furthermore, pharmacokinetics will be determined. Manual blood samples will be used to determine the arterial input curve and to calibrate and correct it for plasma-to-whole blood concentration ratios and labelled protein binding fractions, thereby generating a protein binding corrected, arterial plasma input function. Full-kinetic quantitative analysis will be performed using 1-tissue and both irreversible and reversible 2-tissue compartment models, all with an additional blood volume fraction parameter consisting of whole-blood activity. Pharmacokinetic parameters will be extracted, such as the volume of distribution (VT). Furthermore, several simplified uptake metrics will be

derived, such as several semiquantitative parameters (standardized uptake values). In this way, we are able to determine which model best describes the kinetics of the radiotracer and which simplified and/or semiquantitative parameter correlates best for accurate quantification of [18F]fluoro-PEG-folate uptake in whole-body PET/CT scans.

Secondary outcome

The secondary objective of the study is to investigate the sensitivity and specificity of the [18F]fluoro-PEG-folate PET/CT scan for the detection of metastatic disease in epithelial ovarian cancer. This will independently be determined qualitatively as well as quantitatively by two nuclear medicine physicians, using the Peritoneal Cancer Index (PCIPET/CT). This PCI indicates the presence of large (> 5 cm), moderate (0.5-5 cm), small (< 0.5 cm) or no involvement in 13 abdominal regions. The assessment of para-aortic and pelvic lymph nodes is not included in the PCI, but will be added to the CRF. Semiquantitative parameters will be obtained by semi-automatic tumor segmentation based on, for example, a threshold value method. Regions of interest (ROIs) determination will be performed by an investigator who is blinded for the results of immunohistochemical data. In addition, the conventional CT-scan made during routine clinical work-up will be scored by two independent radiologists, also using the PCI (PCICT). Preoperative PET-positive lesions and routine conventional CT findings will be compared on the basis of the PCI and a per-lesion based analysis. Postoperative histological findings will be regarded as the gold standard for presence, magnitude and localization of metastatic lesions. Imaging signal and histologically proven malignancy will

be scored as a dichotomous variable (yes/no, 2x2 table). The number of true positive, true negative, false positive and false negative lesions will be reported. If feasible, whole mount tissue sections will be obtained to correlate immunohistochemical FR expression to [18F]fluoro-PEG-folate uptake in the primary tumor as seen on the FR-targeted PET/CT images.
The sensitivity is defined as the proportions of [18F]fluoro-PEG-folate PET positive lesions to the total number of histologically confirmed EOC lesions (with a 95% confidence interval). The specificity is defined as the proportions of [18F]fluoro-PEG-folate PET negative lesions to the total number of lesions without tumor involvement (with a 95% confidence interval). The location and magnitude of these lesions will be taken into account. Positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy will be calculated as far as possible in this small study population.

Study description

Background summary

Clinical relevance
Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological cancer in developed countries. In the Netherlands, there are annually 1300 newly diagnosed ovarian cancers and 1100 women die from this disease. The high mortality rate in EOC is due to the fact that 75% of women present with advanced stage disease. In these women, treatment consists of cytoreductive surgery, either preceded by neoadjuvant chemotherapy (NACT), and subsequently followed by adjuvant chemotherapy. Completeness of surgery is the most significant prognostic variable for survival. Cytoreductive surgery therefore aims to achieve resection of all visible lesions. During surgery however, gynecologic oncologists must rely on naked eye visual inspection and palpation, potentially leading to inaccurate cancer resections.
Whether NACT is administered prior to cytoreductive surgery in patients with advanced stage EOC is determined on the basis of the patient*s performance

status and surgical resectability as estimated on computed tomography (CT) scan. Despite the fact that the overall sensitivity of a CT scan is 85-93%, it is merely 11-37% for the detection of tumors located in the subdiaphragmatic space, omentum, root of mesentery and serosal surface of the small bowel. It is the involvement of these sites that signify irresectability. Consequently, 33-39% of patients undergo unnecessary laparotomy. Diagnostic laparoscopy prior to cytoreductive surgery has shown to lower this rate to 10%, but this method is invasive and its utility is hampered by bulky tumors and adhesions. Lastly, diffusion-weighted magnetic resonance imaging (DW-MRI) seems promising, but further research is needed before this modality can routinely be used.

Molecular imaging using agents that specifically target EOC will allow for improved preoperative tumor detection. A suitable target for tumor-targeted molecular imaging of metastatic lesions in EOC is folate receptor (FR). FR is overexpressed in 90-95% of EOCs and their corresponding peritoneal, omental and lymph node metastases. In the majority of normal tissues its expression is absent. We previously showed that the use of a folate analogue conjugated to a fluorescent dye in the near-infrared range (OTL38, * = 700-900 nm) led to the detection of 29% additional metastatic lesions that would otherwise not have been detected during cytoreductive surgery.

FR-targeted positron emission tomography (PET) imaging using the 18F]fluoro-PEG-folate PET tracer can aid in the preoperative assessment of metastatic tumor load in patients with advanced stage EOC and may ultimately help selecting patients for either primary cytoreductive surgery or NACT followed by interval cytoreductive surgery. It may thereby ensure that patients will be offered customized treatment and reduce the number of unnecessary laparotomies. Before FR-targeted PET/CT imaging can be implemented in routine clinical work-up in patients with EOC, more information is needed on the safety, tolerability and the biodistribution of the [18F]fluoro-PEG-folate PET tracer as well as the sensitivity and specificity of [18F]fluoro-PEG-folate PET/CT imaging for the detection of metastatic lesions derived from EOC. The current study aims to examine these parameters.

Study objective

Primary objective:
1. To evaluate the safety and tolerability of the [18F]fluoro-PEG-folate PET tracer
2. To determine the pharmacokinetics (protein binding, biodistribution, clearance rate) of the [18F]fluoro-PEG-folate PET tracer

Secondary objectives:
To examine the sensitivity and specificity of [18F]fluoro-PEG-folate PET/CT

imaging for the detection of metastatic lesions in patients with advanced stage EOC.

Study design

A phase I study will be conducted. An exact sample size is not applicable for this study. A total of 15 patients with advanced stage EOC scheduled to undergo cytoreductive surgery will be included at the LUMC. This number is feasible, as each year approximately twelve to fifteen patients with advanced stage EOC will undergo cytoreductive surgery.

After inclusion, 185 MBq of [18F]fluoro-PEG-folate will be intravenously administered. Immediately following injection, an FR-targeted PET/CT scan will be performed. During the PET/CT scan nineteen arterial blood samples (97 mL in total) are taken for pharmacokinetic analyses. Vital signs will be measured. PET images will be independently scored by two nuclear medicine physicians using the Peritoneal Cancer Index (PCIPET/CT). This PCI indicates the presence of large (> 5 cm), moderate (0.5-5 cm), small (< 0.5 cm) or no involvement in 13 abdominal regions. The assessment of para-aortic and pelvic lymph nodes is not included in the PCI, but will be added to the case report form (CRF). The conventional CT-scan made during routine clinical work-up will be scored by two independent radiologists, also using the PCI (PCICT). Within three weeks following the FR-targeted PET/CT, patients will undergo cytoreductive surgery. During surgery, the gynecologic oncologists will determine the PCI (PCIsurgery) using the CRF without knowledge of the results of the FR-targeted PET/CT scan. The PET/CT findings will be presented after initial exploratory laparotomy but before cytoreductive surgery to allow for a *second look*. The suspect lesions on the FR-targeted PET/CT will be identified and marked on the CRF. The PET-positive lesions that were neither detected by the conventional CT scan nor by initial exploration during cytoreductive surgery will remain in situ. These non-resected PET-positive lesions will be reported on the CRF as being clinically suspected of malignancy (yes/no). All suspect lesions identified by the conventional CT scan and/or cytoreductive surgery will be excised, when surgically feasible (standard care). These resected suspect lesions will be reported on the CRF as being PET-positive (yes/no). The resected lesions will then be examined on tumor status by a pathologist specialized in gynecologic oncology. Immunohistochemical staining for FR expression on the resected tissues will be performed. FR-targeted PET/CT results will be compared to postoperative histopathology (gold standard; if applicable) and the previously made routine conventional CT scan.

Intervention

• A screening visit including ECG prior to the performance of the [18F]fluoro-PEG-folate PET/CT scan
• Intravenous administration of [18F]fluoro-PEG-folate prior to the

[18F]fluoro-PEG-folate PET/CT scan
• An ascites drainage if a large amount of ascites is present
• Performance of the [18F]fluoro-PEG-folate PET/CT scan
• An extra iv to take blood samples (max. 108 mL in total) and an ECG following the [18F]fluoro-PEG-folate PET/CT scan
• A short phone call two and six weeks following the [18F]fluoro-PEG-folate PET/CT scan, respectively

Study burden and risks

Patients participating in this study will undergo PET/CT imaging and will thus be exposed to radiation. Additionally, although the investigational product has already been used in humans, it is possible that unknown side effects occur. For complete pharmacokinetic analysis and protein binding analysis, arterial blood sampling (97 mL) will be performed. The additional burden of patients is acceptable as only one visit, twice an electrocardiography (ECG) and extra blood sampling is required (max. 108 mL in total) to participate in this study. The extent of risks associated with participation in this study is considered relatively low. .

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 with radiologically FIGO stage IIIB/IIIC EOC based on the conventional CT scan who are
• scheduled to undergo primary cytoreductive surgery and
a) in whom EOC is histologically proven, or
b) in whom EOC is cytologically suspected and a serum CA125/CEA ratio > 25 is found
or
• treated with neoadjuvant chemotherapy (NACT) and are scheduled to undergo interval cytoreductive surgery and
a) in whom EOC is histologically proven, or
b) in whom EOC is cytologically suspected and a serum CA125/CEA ratio > 25 was found before NACT
c) and with radiologically FIGO stage IIIB/IIIC EOC based on the response evaluation CT scan after NACT

Exclusion criteria

1. Women younger than 30 years of age (in accordance with the guidelines of the Netherlands Commission on Radiation Dosimetry, as the total radiation dose will be 7.2 mSv)
2. Patients who previously underwent primary laparotomy and in whom complete or optimal cytoreduction was not considered feasible.
3. Contraindication for PET (pregnancy, lactating or severe claustrophobia)
4. Thrombocytopenia (platelet count < 100 x 10^9/L) and/or INR > 2
5. Impaired renal function (defined as eGFR < 50 mL/1.73 m2)
6. Impaired liver function (ALT, AST or total bilirubin > 3x upper limit of normal)
7. Clinically significant abnormalities on ECG and/or clinically laboratory test
8. Inability to tolerate lying supine for the duration of a PET/CT examination (~110 minutes)
9. Patients with concomitant malignancy (except basal cell carcinoma of the skin) or any condition that in the opinion of the investigators could potentially jeopardize the health status of the patient
10. Patients not able to comply with the study procedures

11. Patients who did not give informed consent

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-09-2021
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[18F]fluoro-PEG-folate
Generic name:	[18F]fluoro-PEG-folate

Ethics review

Approved WMO Date:	22-02-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	20-05-2021
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2020-000112-29-NL
CCMO	NL72618.058.20