Development of a more sensitive method to predict breast cancer recurrence after 5-years of endocrine treatment making use of diagnostic leukapheresis to detect circulating tumor cells

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Observational invasive

Summary

ID

NL-OMON49077

Source
ToetsingOnline

Brief title
Sibylla

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer, invasive mammary carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: KWF

Intervention

Keyword: circulating tumor cells, diagnostic leukapheresis, hormonal treatment, primary breast cancer

Outcome measures

Primary outcome

The primary endpoint is a CTC detection rate through the DLA method of 15% in

the 1-3 PLN group and 30% in the >=4 PLN group.

Secondary outcome

- The concordance of the CTC detection rate in DLA product vs the CTC detection

rate in 7.5mL and in 30mL blood samples per patient

- The detection rate of CTCs compared to the detection rate of circulating

tumor (ct)DNA per patient.

- To assess the incidence of lymphedema following DLA using the Lymph-ICF

questionnaire and arm circumference measure.

Study description

Background summary

Adjuvant endocrine treatment (ET) for 5 years is standard for patients with primary hormone receptor positive (ER+) breast cancer. However, recurrences still occur, of which more than 50% occur after 5 years ET. Extended adjuvant endocrine therapy (EET), up to 10-15 years, increases disease free survival (DFS). However, there is no robust biomarker predicting late recurrence risk after 5-years ET. The measurement of circulating tumor cells (CTCs) as a reflection of residual disease could possibly serve as such a biomarker. Recent studies showed the prognostic value of CTC enumeration in ER+ lymph node

positive (N+) primary breast cancer patients during and after ET.
Unfortunately, the classic CTC enumeration method using 7.5 mL of blood is not sensitive enough as disease recurrence also occurred in patients without detectable CTCs. To measure residual disease through more sensitive CTC detection, screening of a larger blood volume is desired. CTC enumeration in 30 mL of blood yielded a higher percentage of patients who had >=1 CTC than in 7.5 mL of blood, which increases sensitivity and specificity. However, the robustness of this test is weak due to stochastic variation inherent to the low CTC numbers found.
A technique to greatly increase the screened blood volume is called Diagnostic Leukapheresis (DLA). During DLA, 2.5-5L of blood is passed through a centrifuge, which isolates peripheral blood mononuclear cells (PBMCs) as well as CTCs from the blood, which is returned to the patient. Preliminary results have shown that this procedure increases the sensitivity of CTC detection substantially by 500-1000. We therefore hypothesize that CTC detection through DLA improves the detection rate among ER+, N+ primary breast cancer who have received 5 years of adjuvant endocrine therapy and will be a promising technique for risk classification in this patient group.

Study objective

The primary objective of this study is to demonstrate that our DLA-based method is promising enough to detect CTCs in ER+, N+ primary breast cancer patients after 5 years ET. Simultaneously, other methods (CTC detection in 7.5 ml and 30 ml of blood as well as ctDNA detection) will be assessed in this study population and explored how they compare with our DLA-based approach in terms of tumor load detection.

Study design

This is an observational, biomarker study using a Simon-two- stage design

Study burden and risks

All patients will be asked to undergo a single leukapheresis procedure which will take a maximum of 2 hours. A maximum volume of five litre peripheral blood will be processed with the use of an Optia Spectra Cell Separator. Patients do not benefit from this study. The most common adverse events to be expected are pain or bruising at the venipuncture site (1-5%), apprehension or fainting associated with venipuncture (1-5%) and citrate anticoagulant infusion-related symptoms resulting in tingling or buzzing around the mouth or fingers (20-50%). To prevent the latter, all patients will receive intravenous calcium, which reduced the incidence of citrate-related effects by 65 percent in a randomized trial performed by Buchta et al. An infrequent adverse event is fluid imbalance (0.01-0.1%, more likely to occur during long procedures). Specialized apheresis-nurses are trained to recognize and act upon this complication.

Hypotensive or vasovagal reaction will be treated in the standard manner by the attending medical officer. The risk of adverse events associated with LA is considered negligible.

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

1. Female
2. Age >18 years
3. Diagnosed with ER+ Her2-negative lymph node positive, primary breast cancer
4. Received at least 4.5 - 5.5 years of adjuvant ET for breast cancer
including those who are <6 months after finishing endocrine therapy.
5. No clinical signs of locoregional or distant recurrence.
6. At least one adequate peripheral vein in both arms as access for

leukapheresis.
7. Provide written informed consent

Exclusion criteria

1. Prior non-breast malignancies <5 years of inclusion, except for basal or squamous cell carcinoma of the skin
2. Pre-existing lymphedema, quantified by specialist
3. Known hypersensitivity to the used anticoagulant (ACD)
4. Inadequate cardiac function or severe cardiovascular comorbidity (heart failure NYHA class III/IV)
5. Coagulation disorders as defined by one of the following:
NOTE: the use of all types of anticoagulant therapy is permitted
o Coagulation disorder in medical history
o Platelet count < 40 x 10^9/L;
Patients not on anticoagulant therapy which affects PT or APTT if:
o PT > 1.5 x ULN or PT-INR > 1.5 x ULN
o APTT > 1.5 x ULN
Patients who take anticoagulant therapy which affects PT or APTT if:
o PT or APTT > 1.5 x the upper limit of the desired therapeutic window
o Total bilirubin > 2.5 x ULN
6. BMI >= 35 kg/m2

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):	03-11-2020
Enrollment:	87
Type:	Actual

Ethics review

Approved WMO Date:	08-07-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL71855.078.20