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High-resolution contrast-enhanced ultrasound and biological markers to assess the response of triple-negative breast cancer during neoadjuvant chemotherapy

Submission date
18/10/2022

Recruitment status
No longer recruiting

Registration date
09/05/2023

Overall study status
Completed

Last Edited
09/05/2023

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Triple-negative breast cancer (TNBC) accounts for around 10-15% of new diagnoses. These types of breast cancer are not dependent on oestrogen and progesterone or the HER-2 molecule to encourage them to grow and the common treatments to stop the supply of oestrogen to breast cancer cells or newer treatments against the HER-2 molecule can't be used. TNBC tumours tend to be larger than other types of breast cancer with a higher chance of spreading within 5 years of diagnosis. As cancerous tumours get bigger, they try to grow more blood vessels. This happens through a process called angiogenesis. Tumours can also make channels of cancerous cells to get blood into them, called vasculogenic mimicry. Increasing the number of blood-carrying channels may help them spread and vascular mimicry is linked to poorer survival. Modern treatment of TNBC is mainly dependent upon chemotherapy first before surgery because the strong drugs can shrink the cancer completely in up to half of cases. However, it is often not easy to track how the cancer is responding because radiology tests cannot accurately show whether the cancer has reduced. New high-resolution ultrasound technology using tiny injected bubbles (microbubbles) holds the promise of improved monitoring by allowing the blood vessels inside the tumour to be seen. Changes in the blood vessels of the tumour during a course of chemotherapy may even be able to predict how the cancer is going to behave with treatment namely shrink, stay the same or even grow.

This study aims to use the new technology of high-resolution contrast-enhanced ultrasound to look at the size, shape and internal web of blood vessels of TNBC tumours during upfront chemotherapy and watch how they respond to the treatment. By linking the imaging features of the blood vessel network with the microscopic appearances, this research will be able to tell whether cancer blood flow involves normal-type vessels or vasculogenic mimicry. This is relevant because there are already drugs available against the formation of new blood vessels (angiogenesis) but if most of the blood flow is through vasculogenic mimicry then these types of drugs won't work. Little is known about how blood flow through TNBC changes during chemotherapy in actual patients rather than animal models and information from this research could show whether increased blood flow is good or bad when trying to shrink breast cancer

with chemotherapy. At the end of the study, the results should give a good idea of what blood flow patterns and biological markers predict a good response to chemotherapy.

Who can participate?
Female patients aged 18 to 60 years with newly diagnosed triple-negative breast cancer

What does the study involve?
Using high-resolution contrast-enhanced ultrasound and microbubbles injected into a vein, the tiny blood vessels inside the breast tumour will be seen and changes tracked as patients progress through their treatment. The findings will be compared with the standard radiological tests used to monitor cancer response to chemotherapy and the results of surgery. The imaging results will be linked with biological findings of cancer growth, new blood vessel formation and vasculogenic mimicry from biopsies (samples) taken from the tumours at diagnosis and set time points during the chemotherapy, as well as the results of surgery. As 10-20% of TNBC patients have a mutation in the hereditary breast cancer genes BRCA 1 or 2, this research will also see if there is a link between these mutations, cancerous blood vessel changes and cancer shrinkage in the breast. In addition, there is a type of TNBC called basal type that can have a worse outcome and this may be because more blood channels are produced in these tumours. The study will therefore look at this in detail by combining the results of the high-resolution contrast ultrasound with the biological markers of cancer growth and blood vessel formation.

What are the possible benefits and risks of participating?
The number of blood vessels in a tumour at diagnosis and whether they increase or decrease during chemotherapy may affect how well the treatment works. The chemotherapy drugs are carried in the bloodstream and must reach the cancerous cells to take effect. Cancerous tumours may have relatively few blood vessels or 'shut down' new blood vessel formation when subjected to the challenge of chemotherapy and this could result in a poor response with the tumour staying the same size or even increasing. On the other hand, if tumours make lots of new vessels this could allow the chemotherapy drugs to reach the cancerous cells and shrink the breast cancer. High-resolution contrast ultrasound could give this type of information and may help decide which patients would benefit from upfront chemotherapy or have surgery to remove the cancer as their first treatment. Knowing whether the blood supply inside a tumour is made up of normal blood vessels or vasculogenic mimicry could also help use targeted treatment to stop new blood vessels from being made. In the future, microbubbles could even be used to carry chemotherapy drugs and deliver them directly inside the cancer by 'bursting' the bubbles with the ultrasound.
Risks of participation include the risk of intravenous contrast agent use. However, these are widely used and have very few adverse effects in healthy patients. There is also the risk to those who have other medical conditions such as severe heart, lung or kidney disease as these patients should not have intravenous contrast, but these patients are unlikely to be offered NACT because of poor tolerance. Therefore, all those fit enough for chemotherapy should be eligible for the study. There is a further risk of thromboembolic events (clots) during chemotherapy and these patients will need to be withdrawn from the study as this is a further risk for ultrasound contrast agents.

Where is the study run from?
The Maidstone and Tunbridge Wells NHS Breast Unit (UK)

When is the study starting and how long is it expected to run for?
April 2021 to September 2023

Who is funding the study?
1. Breast Cancer Kent (UK)
2. Maidstone and Tunbridge Wells NHS Trust (UK)

Who is the main contact?
Jaideep Rait, j.rait@nhs.net

Plain English summary under review withe external organisation

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
301345

Protocol serial number
IRAS 301345

Study information

Scientific Title
Imaging of tumour microvasculature using high-resolution contrast-enhanced ultrasound together with markers of proliferation/angiogenesis/vascular mimicry to characterise the response to neoadjuvant chemotherapy in triple-negative breast cancer

Acronym
TNBC-CEUS

Study objectives
The project aims to utilize high-resolution contrast-enhanced ultrasound (CEUS) as a tool to image the microvasculature of triple-negative breast cancer (TNBC) tumors in patients undergoing neoadjuvant chemotherapy (NACT) and correlate imaging with established markers of angiogenesis, proliferation and vasculogenic mimicry.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/05/2022, West of Scotland Research Ethics committee (Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0212; WosRec1@ggc.scot.nhs.uk), ref: 22/WS/0045

Study design
Observational single-centre cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Triple-negative breast cancer (TNBC)

Interventions
High-resolution CEUS will be performed using an intravenous contrast agent to quantify tumor size and microvessel density and will be compared to conventional imaging techniques at three designated points; 1) prior to NACT, 2) between cycles 2 & 3 of NACT and 3) upon completion of NACT. At two separate timepoints (diagnosis & between cycles 2 & 3) each patient will have 11G core biopsies of the tumour with immunohistochemistry to quantify markers of proliferation, markers of angiogenesis and features of vasculogenic mimicry. These markers will be repeated on any residual disease retrieved by surgery.

Intervention Type
Other

Primary outcome(s)
1. Imaging parameters (tumour vascularity, flow velocity and distribution, complexity of vascular structures [fractal dimension], regularity of vascular flow and vessel pulsatility) assessed using the high-resolution CEUS test and compared with the results of standard imaging prior to NACT, between cycles 2 & 3 of NACT and upon completion of NACT
2. Immunohistochemical markers of angiogenesis, proliferation and vascular mimicry measured using standard immunohistochemistry techniques prior to NACT, between cycles 2 & 3 of NACT and upon completion of NACT

Key secondary outcome(s))
1. Phenotypes of all cases determined using immunohistochemistry and subtype analysis prior to NACT
2. Germline mutations and somatic BRCA1/2 gene mutations assessed using panel sequencing prior to NACT

Completion date
30/09/2023

Eligibility

Key inclusion criteria
1. Provision of written informed consent
2. Biologically female aged 18 to 60 years
3. Histologically confirmed TNBC with planned NACT
4. In the investigator's opinion, adhering to the trial recommendations and governance

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
60 years

Sex
Female

Key exclusion criteria
1. Cannot provide consent
2. Previous ipsilateral breast cancer with chemotherapy
3. Pregnant or breastfeeding
4. Locally advanced or inflammatory breast cancer
5. Metastatic breast cancer
6. Allergy to ultrasound contrast
7. TNBC subtype associated with good prognosis (adenoid cystic carcinoma, secretory carcinoma, acinic cell carcinoma, carcinoma with apocrine differentiation, low-grade metaplastic carcinoma and carcinoma arising in micro glandular adenosis)
8. Right to left cardiac shunt
9. Uncontrolled hypertension
10. Severe pulmonary hypertension
11. Recent thromboembolism
12. Hypercoagulation disorder
13. Adult respiratory distress syndrome

Date of first enrolment
11/10/2022

Date of final enrolment
01/07/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

Maidstone & Tunbridge Wells NHS Trust
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Sponsor information

Organisation
Maidstone and Tunbridge Wells NHS Trust

ROR
https://ror.org/02yq33n72

Funder(s)

Funder type
Charity

Funder Name
Breast Cancer Kent

Funder Name
Maidstone and Tunbridge Wells NHS Trust

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Mr Jaideep Singh Rait (j.rait@nhs.net) with all data suitably anonymised. Consent is obtained from participants to share data in the future for relevant studies. The data would be made available on an individual request basis after assessment by the trial management group.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No

Participant information sheet	version 2	26/04/2022	19/10/2022	No	Yes