T&T trial: adding Testosterone to Tamoxifen in male breast cancer patients

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Primary Objective: To assess the safety profile (AEs, SAEs) on combined treatment with tamoxifen and testosterone.Secondary Objectives:• AR to ER ratio on baseline FES- and FDHT-PET imaging (assessed per lesion and per patient by quantitative...

Ethical review	Approved WMO
Status	Completed
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON51371

Source
ToetsingOnline

Brief title
T&T trial

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
male breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: male breast cancer, Tamoxifen, Testosterone

Outcome measures

Primary outcome

Safety profile, defined as the number of AEs and SAEs that occur while on tamoxifen and testosterone treatment.

Secondary outcome

• AR to ER ratio on baseline FES- and FDHT-PET imaging (assessed per lesion and per patient by quantitative analysis using standardized uptake values (SUV)) and/or tumor tissue (assessed by percentage of ER and AR expression).

• Treatment response on 8 weeks FDG-PET/CT (assessed per lesion and per patient by quantitative analysis using standardized uptake values (SUV).

• Relation between baseline imaging and tumor characteristics to treatment response.

• Difference in adverse events between the two testosterone dosages.

Study description

Background summary

Male breast cancer (BC) is rare and usually shows favorable characteristics with expression of the estrogen-, progesterone- and androgen receptor (ER, PR and AR), but not the human epidermal growth factor-2 receptor (HER2). In ER+ BC, contrary to triple negative BC, the AR appears to function as tumor suppressor. Recently, in preclinical ER+ BC models growth inhibition was shown when an androgen agonist was combined with standard ER modulator tamoxifen. Therefore, this could potentially be a rational treatment option for patients with ER+ BC as well. However, earlier studies in female BC patients showed considerable side effects due to virilization, and treatment with androgen agonists was subsequently abandoned. No data exist in male BC patients, but it

is highly conceivable that virilization is not as concerning in male BC patients and could potentially even be considered as beneficial. Recent data suggest that the ratio of AR to ER in the tumor is relevant for response to AR and ER targeting treatments. Assessment in tumor tissue however can only reflect one part of one tumor lesion. Whole body ER and AR expression can be visualized using 16α-[18F]fluoro-17βoestradiol (FES) positron emission tomography (PET) and [18F]fluoro-dihydrotestosterone (FDHT) PET. These scans potentially allow fine-tuning of combined treatment with an androgen agonist and tamoxifen. Ultimately, this could lead to a new, additional combined endocrine approach in the treatment of male BC patients. Particularly regarding the expected favorable (side) effects of this combination in men, this could contribute to improved quality of life in male BC patients.

Study objective

Primary Objective: To assess the safety profile (AEs, SAEs) on combined treatment with tamoxifen and testosterone.
Secondary Objectives:
• AR to ER ratio on baseline FES- and FDHT-PET imaging (assessed per lesion and per patient by quantitative analysis using standardized uptake values (SUV) and/or tumor tissue (assessed by percentage of ER and AR expression).
• Treatment response on 8 weeks FDG-PET/CT.
• Relation between baseline imaging and tumor characteristics to treatment response.
• Difference in adverse events between the two testosterone dosages.
• Increase in free testosterone levels, related to treatment response and toxicity.
• Monitoring of blood hematocrite, related to testosterone treatment.
• CtDNA for ER mutation analysis and CTCs (for ER and AR expression) at baseline, prior to cycle 2 and 3, related to response and FES- and FDHT PET imaging.

Study design

This is a concise single arm, feasibility study, which will be executed in the University Medical Center Groningen, The Netherlands. Male patients with metastatic BC (n=6) are eligible for this study after at least 1 line of conventional endocrine therapy.

Intervention

After the baseline imaging with FES- and FDHT-PET is completed, tamoxifen 20mg 1dd1 (standard dosage) plus testosterone (Androgel®) will be started. The first 3 patients will receive 25mg testosterone once daily (half the standard starting dosage for male hypogonadism). If this is well tolerated after 3 weeks, the dosage will be increased to 50mg once daily. Out of precaution, the

safety profile of the 50mg dosage in the first 3 patients will be evaluated after all 3 patients have received 50mg testosterone for 8 weeks, prior to proceeding to the next 3 patients. Patients will be treated with tamoxifen and testosterone until disease progression or unacceptable toxicity.

Study burden and risks

At baseline two additional visits for FES- and FDHT PET imaging are required. FES- and FDHT PET imaging, with a standard 3 Mbq/kg injection dose, lead to an additional radiation exposure of 4.6 and 3.6 mSv respectively. This is comparable to a standard FDG PET for each scan. Further participation will be embedded in standard care, meaning no additional drawing of blood, site visits or physical examinations will be required in addition to those already required for standard care. Tamoxifen is part of the standard treatment strategy in male BC and is known to induce toxicity such as hot flashes and loss of libido. Testosterone is known to induce virilization. Based on the well-known safety profile of tamoxifen and testosterone separately in men, and the previous data of combined tamoxifen and AR agonists in female BC patients, showing no additional toxicity other than expected based on the separate compounds, no unexpected toxicity of the combination is expected in male BC patients. Furthermore, it is conceivable that the combined treatment is better tolerated (and possibly more effective) than standard tamoxifen alone in men with BC.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male
2. A history of proven ER+ (>10% of cells), AR+ (>10% of cells), and HER2- metastatic BC
3. Tumor progression after at least one line of conventional endocrine therapy (tamoxifen, AI, fulvestrant, CDK4/6, ±LHRH analogue).
4. Age >= 18 years
5. Adequate hematological, renal and liver function as follows:
• Absolute neutrophil count > 1.5 x 109/L
• Platelet count >100 x 109/L
• White blood cell count >3 x 109/L
• AST and ALT <2.5 or <5.0 in case of liver metastases x upper limit of normal (ULN)
• Creatinine clearance >50mL/min
• Prothrombin time, partial thromboplastin time and INR <1.5 x ULN
6. Written informed consent

Exclusion criteria

1. History of prostate, testicular or liver cancer
2. Patients already using testosterone supplements
3. Patients using medication with anti-androgenic effects (e.g. spironolactone)
4. Elevated PSA (>4µg/L) or severe urinary tract problems (as defined with a Prostate Symptom Score >19). Patients with known BRCA mutation and PSA *3 µg/L will be referred to the urologist for prostate cancer screening, and can participate if they have no signs of prostate cancer.
5. Hematocrit >50%
6. Patients with uncontrolled hypertension, diabetes mellitus or other significant cardiovascular morbidity.
7. Patients with recent history of coronary artery disease or trombo-embolic events within 6 months prior to screening
8. Severe concurrent disease, infection, co morbid condition that, in the

judgment of the investigator would make the patient inappropriate for enrollment
9. Visceral crisis and/or rapid progression necessitating chemotherapy
10. Previous allergic reaction to androgen agonists
11. Contra-indication for PET imaging
12. Tamoxifen or fulvestrant treatment <5 weeks prior to FES-PET.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-11-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Testosterone/Androgel
Generic name:	Testosterone/Androgel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	04-04-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	20-10-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-02-2024
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
EudraCT	EUCTR2021-002170-72-NL
CCMO	NL79433.042.22
Other	volgt