Chemotherapy Adjuvant Study for women at advanced Age (CASA); Phase III Trial Evaluating the Role of Adjuvant Pegylated Liposomal Doxorubicin (PLD, Caelyx®, Doxil®) for Women (age 66 years or older) with Endocrine Nonresponsive Breast Cancer Who Are NOT Suitable for Being Offered a *Standard Chemotherapy Regimen*

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON31071

Source
ToetsingOnline

Brief title
CASA

Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Age related factors

Synonym
breast cancer, mammacarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: International Breast Cancer Study Group (IBCSG)
Source(s) of monetary or material Support: IBCSG;Zwitserse onderzoeksgroep

Intervention

Keyword: breast cancer, elderly, pegylated liposomal doxorubicin

Outcome measures

Primary outcome

Breast cancer free interval (events are reappearance of invasive breast cancer

at any site including contralateral breast cancer).

Secondary outcome

Tolerability (treatment completion); Adverse events; Quality of life;

Disease-free survival (includes second malignancies and deaths); Sites of

failure; Second (non-breast) malignancy; Overall survival; Competing causes of

death

Study description

Background summary

The appropriate use of adjuvant chemotherapy for elderly women with breast carcinoma remains controversial. Efficacy data in women aged > 70 years are

scarce, resulting in a lack of clear guidelines for patients in this age group.
Several studies have demonstrated decreasing use of chemotherapy with age, with no age-related differences in either the drug regimens recommended or patient acceptance rates for adjuvant therapy. In the 1998 Overview Analysis conducted by the Early Breast Cancer Trialists* Collaborative Group (EBCTCG), few women aged 70 or over had been studied. No clinical trials have been specifically conducted in elderly women with an endocrine nonresponsive early breast cancer in order to define the best adjuvant treatment in this subpopulation.
Thus, a therapeutic dilemma exists when a woman at advanced age presents with an endocrine nonresponsive early breast cancer. Relapses of breast cancer may occur earlier in patients with endocrine nonresponsive disease compared to those with hormone receptor-expressing tumors, even when axillary nodes are negative at presentation. This provides a rationale for reducing the risk of relapse even when life expectancy is less than decades.
Such dilemma does not exist if the patient is biologically (and functionally) young, and a *standard* chemotherapy regimen may be offered with no concern. The physician may decide not to offer a relatively frail patient any treatment, for fear of possible subjective or severe toxic effects of chemotherapy.
Typically, however, these patients are treated in a rather heterogeneous way by arbitrarily reducing doses or modifying schedules of adjuvant chemotherapy regimens that were studied in younger women. This trial is therefore important because it is designed to test a reasonably tolerated cytotoxic regimen for a patient subpopulation uniformly treated within a randomized trial.
The choice of the population (endocrine nonresponsive) is advantageous because the magnitude of chemotherapy effect for this postmenopausal cohort is likely to be quite large, similar to the effect observed for premenopausal patients with similar biological tumor characteristics. Avoiding dilution with patients having endocrine responsive tumors (even those with high number of axillary lymph nodes involved) maximizes the chance to observe a benefit in the shortest time with the lowest number of patients.

Study objective

The overall aim of the CASA trial is to investigate the role of PLD as adjuvant chemotherapy for older postmenopausal women for whom chemotherapy is indicated, but standard regimens, derived from trials in younger women, are assumed to be too toxic or inconvenient. The stratified analysis combining the results of both randomization options will provide the primary evidence on the effectiveness of PLD. This analysis will assess PLD versus non-PLD-containing control groups (either nil or CM). In addition, analyses will be conducted separately for each of the two randomization options (adjusted for multiple comparisons) to
assess each of the individual pair-wise contributions to the overall result.

Study design

Some of the investigators are likely to choose no adjuvant cytotoxic therapy as a standard for frail patients at advanced age, while others will prefer to offer some treatment for all patients with endocrine nonresponsive disease. In order to take into consideration both attitudes towards the same problem, the International Breast Cancer Study Group (IBCSG) has designed a randomized trial, the CASA trial, with two individual complementary options, in order to investigate the role of adjuvant cytotoxic chemotherapy for postmenopausal women at advanced age with endocrine nonresponsive early breast cancer. Caelyx® (Doxil®), a pegylated liposomal doxorubicin (PLD), was chosen as the experimental treatment because it has been shown to be active in advanced breast cancer and is well tolerated.
These two complementary randomization options are tailored to the investigator's decision and/or the patient*s preference about what would constitute an appropriate control treatment group for the individual patient, thus enabling the physician to express his or her own attitude and/or belief towards adjuvant treatments in this subpopulation. Because of the separate designs, at the time of
randomization the investigator will be asked to select one of the two andomization Options.
This trial requires a rather large number of patients from a rather small subpopulation of breast cancer patients. Although the incidence of breast cancer in elderly women is quite high, it is estimated that only 15% will have a receptor negative (no expression of estrogen receptor [ER] and progesterone receptor [PgR]) disease. Thus, a satisfactory accrual can only be reached with an international collaboration and participation around the world.

Intervention

Pegylated Liposomal Doxorubicin versus nil, is designed for patients who, according to the treating physician and/or to the patient's preferences, are candidates to receive no adjuvant therapy.

Pegylated Liposomal Doxorubicin versus low dose, metronomic cyclophosphamide and methotrexate (CM), is designed for patients who, according to the treating physician and/or to the patient's preferences, should receive some adjuvant treatment.

Study burden and risks

minimal risc, based on standard treatment

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Women aged 66 years or older with histologically proven, resected breast cancer.
- Patients must not be candidates for endocrine therapy or standard chemotherapy regimen.
- Performance status (ECOG) 0-2.
- Patients must have endocrine nonresponsive tumors. (The recommended definition of endocrine nonresponsive: ER less than 10% of cells stained positive by immunohistochemical evaluation. If PgR is done, it should also be less than 10% of cells stained positive by immunohistochemical evaluation.)
- The tumor must be confined to the breast and axillary nodes without detected metastases elsewhere.
- Patients with synchronous (diagnosed histologically within 2 months) bilateral invasive breast cancer are eligible if all tumors are endocrine nonresponsive.
- Patients must have had surgery for primary breast cancer (with or without axillary clearance) with no known clinical residual loco-regional disease.
- Margins must be negative for invasive breast cancer and DCIS.
- Patients should be randomized and start treatment as close to definitive surgery as possible; within 6 weeks is recommended and not more than 16 weeks (from last surgery in

case of bilateral breast cancer).
- Adequate bone marrow, renal, and hepatic function
- Adequate cardiovascular function

Exclusion criteria

- Patients with locally advanced inoperable breast cancer including inflammatory breast cancer, supraclavicular node involvement, or enlarged internal mammary nodes (unless pathologically negative).
- Patients with a history of any prior ipsilateral or contralateral invasive breast cancer.
- Patients with previous or concomitant malignancy diagnosed within the past five years. Patients with adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, contra- or ipsilateral in situ breast carcinoma are eligible regardless of the date of diagnosis.
- Patients with other non-malignant uncontrolled systemic diseases that would preclude trial entry in the opinion of the investigator. Specifically not eligible are patients with uncontrolled active infection, chronic infection such as active HBV or HCV.
- Patients with myocardial infarction, pulmonary embolism or deep venous thrombosis within 6 months prior to randomization.
- Patients with significant malabsorption syndrome or disease affecting gastrointestinal tract function.
- Patients with at least one of the so-called *geriatric syndromes*: dementia, delirium, major depression (as diagnosed by a psychiatrist), recent falls, spontaneous bone fractures, neglect, and abuse.
- No hormone replacement therapy (HRT).
- No prior neoadjuvant or adjuvant therapy for breast cancer. Note: Radiotherapy is allowed prior to randomization.
- Raloxifene, tamoxifen, or other SERM must be discontinued at least 4 weeks before randomization.
- No hormonal therapy, except steroids for adrenal failure, hormones for non-breast cancer related conditions (e.g., insulin for diabetes), or intermittent dexamethasone as an antiemetic.
- No treatment with bisphosphonates, except for the treatment of osteoporosis

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-06-2007
Enrollment:	35
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Caelyx
Generic name:	pegylated liposomal doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Endoxan
Generic name:	cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MTX
Generic name:	methotrexate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	07-06-2007
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)

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	EUCTR2005-003434-18-NL
ClinicalTrials.gov	NCT00296010
CCMO	NL17683.094.07