Prospective evaluation of the predictive value of a circulating tumor cell (CTC) sensitivity profile to Cisplatin chemotherapy in metastatic breast cancer patients

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The aim of this study is to prospectively explore the predictive value of a cDDP-sensitivity profile determined in CTCs of metastatic BC patients previously treated with at least antracycline- and taxane-based chemotherapy.

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

Summary

ID

NL-OMON44123

Source
ToetsingOnline

Brief title
CTC-cDDP

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Metastatic breast cancer, metastatic mammary cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting A Sisters Hope (borstkanker organisatie)

Intervention

Keyword: Breast Cancer, Circulating Tumor Cells, Cisplatin

Outcome measures

Primary outcome

Response rate (RR) (complete response (CR) and partial response (PR)) according to RECIST version 1.1 following 4 cycles of cDDP in the three groups of patients (5 or more CTCs/7.5 mL of blood and a favorable cDDP-sensitivity profile, *5 CTCs/7.5 ml and an unfavorable CTC cDDP-sensitivity profile and <5 CTCs/7.5 mL of blood).

Secondary outcome

- Exploratory analyses assessing the time to treatment switch (TTS), overall survival (OS) and cDDP toxicity in the three groups.

- Retrospective comparison of the 96 gene CTC panel expression profiles between cDDP responders and non-responders following the fourth cDDP cycle (regardless of the patients* cDDP sensitivity profile)

- The exploration of a possible association between a functional assay for predicting homologous recombination deficiency in metastatic tissue and clinical outcome

- The accordance between the CTC cDDP-sensitivity profile and a metastatic tissue cDDP-profile.

Study description

Background summary

Despite significant progress, there is a high need for new effective systemic treatments for advanced/metastatic breast cancer (BC) patients. Cisplatin (cDDP) is used in many tumor types but not in unselected BC patients. In old studies (± 1980s), cDDP monotherapy, given to highly pretreated patients, yielded response rates (RR) of maximum 21% and PFS of 3*4 months. Also, cDDP-containing combination regimens given to pretreated metastatic BC patients have not greatly improved outcomes. In addition, cDDP is associated with relevant toxicity, consisting of nausea and vomiting, nephrotoxicity and neurotoxicity. Fortunately, due to decades of acquired experience with cDDP and improved anti-emetics, cDDP associated toxicity is nowadays more manageable. However, due to the availability of effective and less toxic newer chemotherapeutical and targeted agents, cDDP is not considered standard therapy in unselected BC patients.

Recently, the use of cDDP in BC has regained interest. Several attempts have been made to identify patients who are likely to benefit from cDDP-based treatment based on primary tumor characteristics such as mutations, overexpression and promotor hypermethylation of BRCA1, p53 mutations, so-called triple-negative disease and expression of specific microRNAs. Since data from prospective clinical trials exploring the use of the previously mentioned factors is lacking, there is still an unmet need for factors identifying BC patients likely to benefit from cDDP. If available, cDDP could add an extra available anti-tumor agent for a particular subgroup of BC patients.
One potential pitfall that may cause the previously mentioned factors to be less reliable is the fact that they all have been determined on primary tumor tissue. It is becoming increasingly clear that the characteristics of the primary tumor and metastases may differ, while systemic treatment and genomic instability further augments these differences over time. As a result, primary tumor material obtained at diagnosis is unlikely to reliably represent characteristics of metastases. Unfortunately, tumor tissues of metastatic lesions are hard to obtain, as taking biopsies is often a painful and cumbersome procedure.

Circulating tumor cells (CTCs) are tumor cells that circulate in the peripheral blood of cancer patients and are thought to represent features of metastases better than the primary tumor does. In addition, CTC counts have been correlated with clinical outcome in metastatic BC. Besides that, molecular characterization of CTCs holds great promise as a tool to personalize medicine.
We have recently developed a panel of 96 genes, of which 55 mRNAs and 10 miRNAs are CTC-specific, which can be reliably measured in CTCs enabling detailed CTC characterization. From these 96 genes, we identified 23 genes that predict cDDP

sensitivity and resistance in our panel of 42 BC cell lines. Potentially, determination of this gene expression profile in CTCs of BC patients will enable the identification of BC patients responding to cDDP.

Study objective

The aim of this study is to prospectively explore the predictive value of a cDDP-sensitivity profile determined in CTCs of metastatic BC patients previously treated with at least antracycline- and taxane-based chemotherapy.

Study design

Patients with metastatic breast cancer, pretreated with anthracycline and taxanes, will be included in this phase II study. Of all patients, 20 mL blood will be drawn at baseline for CTC enumeration and molecular characterization. Based on the patients* CTC count and the cDDP-sensitivity gene expression profile 3 groups will be identified: a group consisting of patients with *5 CTCs with a favorable cDDP-sensitivity profile, a group consisting of patients with *5 CTCs but with an unfavorable cDDP-sensitivity profile and a group comprising patients with <5 CTCs. Inclusion will continue until 10 patients with * 5 CTCs and a favorable cDDP-sensitivity profile have been included. In an ongoing study, 11% of metastatic breast cancer patients have *5 CTCs and a favorable cDDP-sensitivity profile, rendering that in total approximately 100 patients will be accrued for CTC enumeration and for the determination of the cDDP-sensitivity profile. All patients will receive 3-weekly cDDP at 70 mg/m2 for a maximum of 6 cycles.

Intervention

Three interventions are considered as study-specific:
1) the blood collection for CTC enumeration and characterization
2) the administration of cDDP (though cDDP is also frequently given to this patient category in daily clinical practice)
3) in patients consenting to this part of the study: a metastatic tissue biopsy

Study burden and risks

A potential risk of cDDP administration is toxicity. We do not expect the risk of cDDP-toxicity to be significantly worse than the risk of toxicity with alternative/comparable chemotherapeutic agents that are also used in daily clinical practice for this indication.

In the optional part of the study, patients are asked if they are willing to undergo a biopsy of a metastatic lesion. The risks associated with the performance of a biopsy are usually mild. In some cases, patients will have to be observed in the hospital for some hours after the biopsy has taken place.

All patients have been informed about these procedures by their treating physician, furthermore, the patient information file states these procedures as well.

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

* Female patient with metastatic breast cancer who has been pretreated with at least anthracycline and taxane-based chemotherapy in the adjuvant and/or metastatic setting ;* Measurable disease according to RECIST 1.1, ie at least one measurable lesion on CT-scan where the longest diameter in the plane of measurement is a minimum size of 10mm;* Age * 18 years;* WHO performance status *2;* Adequate hematological functions defined as ANC * 1.0 x 109/L, platelets * 100 x 109/L;* Adequate renal function defined as creatinin clearance * 60 mL/min (Cockcroft Gault);* Patients with reproductive potential must use a reliable

method of contraception;* Written informed consent

Exclusion criteria

* Other anticancer chemotherapy, use of biological response modifiers, or immunotherapy within two weeks prior to treatment start. Hormonal antitumor treatment within one week prior to treatment start. ;* Hearing loss of at least Common Terminology Criteria for Adverse Events (CTCAE) grade 2;* Neuropathy of at least CTCAE grade 2;* Pregnant or lactating patients;* Serious illness or medical unstable condition prohibiting adequate treatment and follow-up ;* Symptomatic CNS metastases (the presence of at least one key symptom in combination with radiologic evidence (positive contrast-enhanced CT or MRI of the brain));* History of psychiatric disorder that would prohibit the understanding and giving of informed consent or that would prohibit adequate follow-up

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-06-2013
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-01-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2016
Application type:	Amendment
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

ID: 24910
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-005395-34-NL
CCMO	NL42824.078.12
OMON	NL-OMON24910

Study results

Date completed: 28-02-2019

Actual enrolment: 67

Summary results
Trial is onging in other countries