Autophagy inhibition using hydrochloroquine in breast cancer patients: a pilot study

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

Summary

ID

NL-OMON34049

Source
ToetsingOnline

Brief title
HCQ TRIAL

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: autophagy, hydroxychloroquine, hypoxia

Outcome measures

Primary outcome

-

Secondary outcome

-

Study description

Background summary

In response to various stresses, cells can launch a process of *self-eating*, termed autophagy. Thereby, components of the cell are catabolically digested via specific lysosomes called autophagosomes, to provide the cell with energy and other necessary factors to serve as a temporary survival mechanism (Chen et al. 2010).
Two major stressors that can be evaded by autophagy are important for cancer progression and treatment sensitivity:
1. cells can respond with autophagy to cytotoxic treatment such as chemo- or endocrine therapy, thereby leading to treatment insensitivity (Kondo et al. 2005; Chen et al. 2010), and
2. cells can survive severe hypoxia using autophagy (Rouschop et al. 2010), and hypoxic cells themselves are refractory to chemo-, endocrine and radiotherapy.

Thus, tumor cells evade treatment induced cell death by launching a temporary last survival mechanism. Inhibition of this pathway could lead to sensitization for a variety of cancer treatment regimen, or to specific cell killing of tumor associated hypoxic cells that would otherwise be refractory to radiotherapy.

Chloroquine (CQ), N*-(7-chloroquinolin-4-yl)-N,N-diethyl-pentane-1,4-diamine, was discovered in 1934, and has widely been used as an effective and safe anti-malarial and anti-rheumatoid agent since 1947. Later, CQ has been rediscovered as a sensitizer of cytotoxic cancer therapies such as ionizing radiation and chemotherapeutics, although the precise mechanism behind this has remained largely unknown (Solomon and Lee 2009). Most recently, it was discovered that CQ inhibits the process of autophagy by impairment of autophagic vesicle clearance, as CQ accumulates in lysosomal vesicles. This has

now lead to several investigators proposing that CQ or one of its analogs can be used to inhibit the autophagic pathway as an additive to other cytotoxic treatments. Hydrochloroquine (HCQ, Plaquenil) is a CQ derivative with fewer side effects than CQ, which has long been used as anti-malarial and anti-rheumatoid agent. It can be safely used at high doses for extended periods of time. Both CQ and HCQ are under investigation in clinical trials for glioblastoma, small and non-small cell lung cancer, breast cancer, prostate cancer, melanoma, renal cell carcinoma, and pancreatic cancer (for reviews see Solomon and Lee 2009 and Chen et al. 2010). However, the effect of HCQ on tumor tissue, autophagy and/or oxygenation has of yet not been studied in human patients in vivo.

In this pilot study we intend to investigate the effect of HCQ on breast cancer tissues. To this end, breast cancer patients that have given informed consent for participation in the AFTER study (AMO 2010/312), but are not included as their tissue biopsy is found to be ER/PgR negative, will be asked to take 800 mg once, and then 400 mg/day HCQ for 2 to 3 weeks until surgery. We will compare tissue characteristics before and after treatment using HCQ, looking at effects on markers for both hypoxia and autophagy using immunohistochemistry. We expect that after treatment with HCQ tumor cells in hypoxic areas will no longer be able to survive, thus decreasing the number of viable hypoxic cells and increasing the amount of necrosis. This pilot study will serve as a proof of principle for future studies into the effect of autophagy inhibition on treatment sensitivity in breast cancer

Study objective

Primary objective is to assess differences in endogenous hypoxia markers (CA9, PAI-1, VEGF [Rademakers et al. 2008]) and autophagy (LC3b [Rouschop et al. 2010]) before and after short-term pre-surgical treatment with HCQ in breast cancer patients.

secondary objectives will be:
- To compare post-treatment samples with matched (age, stage, histology) samples of patient tissue in our breast tumor bank.
- To assess differences in putative crucial mediators in the autophagy pathway currently under investigation, i.e. TRB3, ATF4, GRP78, LAMP3, etc.

If short-term treatment with HCQ leads to either less hypoxia/more necrosis in tumors, or to signs of decreased autophagy, we intend to set up a larger trial using HCQ as an additive to systemic or locoregional cytotoxic treatment.

Study design

In this pilot study we intend to investigate the effect of HCQ on breast cancer tissues. To this end, breast cancer patients that have given informed consent

for participation in the AFTER study (AMO 2010/312), but are not included as their tissue biopsy is found to be ER/PgR negative, will be asked to take 800 mg once, and then 400 mg/day HCQ for 2 to 3 weeks until surgery. We will compare tissue characteristics before and after treatment using HCQ, looking at effects on markers for both endogenous hypoxia markers (CA9, PAI-1, VEGF) and autophagy (LC3b) before and after treatment with HCQ using standard immunohistochemistry. This pilot study will serve as a proof of principle for future studies into the effect of autophagy inhibition on treatment sensitivity in breast cancer.

Intervention

800 mg once, and then 400 mg/day HCQ for 2 to 3 weeks until surgery.

Study burden and risks

The expected side effects of HCQ during a short treatment period are slight. The research takes place in the regular waiting period before surgery, so no treatment delay occurs. This research can contribute significantly to knowledge about the effect of HCQ on autophagy.

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

•Patients with core-biopsy proven invasive adenocarcinoma of the breast
•Any tumor with a size >= 1cm (NOT inflammatory breast cancer)
•WHO-performance score 0 or 1
•Written informed consent

Exclusion criteria

•Any psychological, familial, sociological or geographical condition potentially hampering adequate informed consent or compliance with the study protocol
•Hampered liver or kidney function
•Serious gastro-intestinal disease
•Neurological disease (including epilepsy)
•Hematological disease
•Psoriasis
•Porphyry
•G6PD deficiency
•Hypersensitivity for quinine
•Use of gold containing drugs, oxyfenbutazone, fenylbutazone, digoxin
•Operation for breast cancer foreseen within 14 days after inclusion in the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-01-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	26-10-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-02-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2010-022842-26-NL
CCMO	NL33914.091.10