

Calcium Electroporation for Treatment of Cutaneous Metastases; randomized double blind phase II study

NCT03628417

Primary Completion Date: 04/06/2019

Last update: 03/10/2019

Last release: 09/24/2019

Introduction

Background

Electroporation is a method that can facilitate transport of molecules across the cell membrane and into the cell by means of electrical pulses. The method can be used with molecules that normally have difficulty passing the cell membrane such as chemotherapy (electrochemotherapy). Electrochemotherapy (ECT) is used in cancer therapy, where chemotherapy is administered intratumoral or intravenous, then followed by electrical pulses applied directly on the tumor. The chemotherapy accumulates in the cancer cells which results in an increased cytotoxic effect. The most used chemotherapeutic drug used in electrochemotherapy is bleomycin. Electrochemotherapy is a well-documented local treatment form for especially cutaneous tumors. Today, the treatment is used mostly in palliative care in more than 140 centres around Europe.

In vitro and *in vivo* studies have shown that the combination of calcium and electroporation is an effective method in killing cancer cells without serious side effects. This new combination opens the possibility of replacing bleomycin with calcium in treatments with electroporation.

Calcium electroporation is a local treatment where calcium is administered intratumoral and followed by electrical pulses applied on the tumor.

Calcium electroporation would be possible to use on patients for whom chemotherapy is contradicted e.g. severe lung functions impairment, pregnant woman etc. Calcium electroporation is a simple and inexpensive cancer treatment that does not involve any administration of cytotoxic chemotherapy, and can be performed by surgeons, radiologists as well as oncologists. Both electroporation equipment and calcium are already being used in the clinic, so the treatment can easily be implemented.

Method

We wish to examine calcium electroporation on patients with cutaneous metastases from any histology and compare the effect with electrochemotherapy. On evaluations on tumor response we want to investigate if calcium can replace bleomycin in the treatment of cutaneous metastases.

To investigate that we use a randomized double blinded phase II study on patients with small cutaneous metastases. The metastases will be randomized into two treatment arms:

1. Intratumoral injection with calcium, followed by electrical pulses.
2. Intratumoral injection with bleomycin, followed by electrical pulses.

Randomization will be done separately on each metastasis

Objectives

Primary Objective

The primary objective is to evaluate and compare response rate of calcium electroporation and electrochemotherapy on cutaneous metastases. Response will be evaluated individual on each treated metastasis by clinical examination and documented by clinical photo before and after treatment. Evaluation is performed according to RECIST-like guidelines.

Secondary Objective

The secondary objective is to register adverse events for calcium electroporation and electrochemotherapy respectively. Adverse Events (AE) and Serious Adverse Events (SAE) will be evaluated and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Tertiary Objective

The tertiary objective is to register if calcium affects the current strength in electroporation treatments. Maximum given current in metastases treated with calcium will be compared to maximum given current in metastases treated with bleomycin.

Trial Design

Trial Design for Treatment of Cutaneous Metastases

It is a randomized double blinded phase II study (adapted from Denmark) comparing the effect of calcium electroporation with ECT with bleomycin on patients with cutaneous metastases of any histology. As calcium and bleomycin are administered intratumoral, only small metastases from 0.5-3cm will be treated. The treatments will be compared in tumor response and adverse events. Treatment will be done in a palliative purpose.

Cancer patients with cutaneous involvement have often several metastases. A maximum of ten metastases will be included per patient. One to six metastases (depending on the patient's number of metastases) will be numbered 1-6 and randomized into one of two treatment arms:

1. Intratumoral calcium followed by electroporation
2. Intratumoral bleomycin followed by electroporation

Randomization will be performed separately on each metastasis, so the patient may receive both treatments. Calcium and bleomycin will be mixed into syringes labeled with numbers according to the metastases and both treating doctor and patient will be blinded to the content of the syringes.

If the patient has more than six metastases, then one to four metastases will be used for biopsy. The treatment of these metastases will be known, and biopsies will be performed before and after treatment. The metastases used for biopsy will not be evaluated on response.

- One to six metastases: All metastases will be evaluated on response, no biopsies.
- Seven metastases: six metastases will be evaluated on response and one metastasis will be used for biopsy before and/or after treatment with calcium.
- Eight Metastases: six metastases will be evaluated on response and two metastases will be used for biopsy before and/or after treatment with calcium and bleomycin respectively.
- Nine Metastases: six metastases will be evaluated on response and three metastases will be used for biopsy before and/or after treatment with calcium and bleomycin respectively.
- Ten Metastases: six metastases will be evaluated on response and four metastases will be used for biopsy before and/or after treatment with calcium and bleomycin respectively.

The treatment will be performed in local or general anesthesia depending on location and number of metastases. Bleomycin/calcium will be administered intratumorally and immediately after the electrode will be placed on the metastasis. The electric pulses are generated using a cliniporator according to ESOPE (European Standard Operating Procedure of Electrochemotherapy). It is a once only treatment and the patients will be followed up with regular clinical controls for six months. At follow up six months after treatment, the randomization code for the one patient will be revealed. If the patient agrees, biopsies will then be taken from an area treated with calcium and an area treated with bleomycin. Last visit will be one year after treatment.

To identify the metastases at follow up visits, the metastases will be marked with a pen, numbered and documented with clinical photos at baseline.

Randomization

The metastases are randomized by block randomization and are done separately in each patient. The randomization is performed by an extern unit, using the computer program nQuery Adviser 7.0. The bleomycin and calcium are mixed and labeled by an extern unit, and since both calcium and bleomycin are transparent and identical in volume, it is possible to label the syringes in a manner to blind the treating doctor. The syringes are labeled with numbers according to the metastases so syringe number '1' goes to metastasis number '1' and so on. The randomization code is kept behind locked doors, and is not accessible to the treating doctor. The randomization code is revealed for each patient after follow up, 6 months after treatment.

The randomization code can be revealed before completion of the investigation, if the investigator believes that the treatment causes so serious unexpected events or reactions, that a continuation of treatment is unacceptable.

As the randomization is done separately in each patient, it is possible to break the code for the individual patient, without breaking the code of the other participants.

Dose

The dose of calcium chloride was amended to 220 mmol/L from 168 mmol/L in this trial.

Volume of calcium chloride is dependent on tumor volume. Smaller tumors should have bigger volume per cm^3 , as smaller tumors are expected to have a bigger loss of injected medicine into the surrounding tissue. The dose volume is calculated according to the 'European Standard Operating Procedure of the Electrochemotherapy (ESOPE)':

Calcium

Calcium chloride 220 mmol/L (9 mg/ml):

- Tumor $< 0,5 \text{ cm}^3$ – 1 ml / cm^3 tumor volume
- Tumor $> 0,5 \text{ cm}^3$ – 0,5 ml / cm^3 tumor volume

Tumor volume = $ab^2\pi/6$ (a=longest diameter, b= longest diameter perpendicular to a)

Bleomycin

Both dose and volume of bleomycin is standard according to ESOPE

Bleomycin 1000 IU/ml:

- Tumor $< 0,5 \text{ cm}^3$ – 1 ml / cm^3 tumor volume
- Tumor $> 0,5 \text{ cm}^3$ – 0,5 ml / cm^3 tumor volume

Tumor volume = $ab^2\pi/6$ (a=longest diameter, b= longest diameter perpendicular to a)

Maximum of injected bleomycin per tumor will be 1500 IU and total dose per treatment 7500 IU. Normal maximum limit for bleomycin is 15.000 IU/ m^2 body surface area.

Bleomycin and calcium chloride are mixed and labeled according to current guidelines. The mixtures will be used in a maximum of 6 hours after mixing.

The Electrical Pulses

The generation of electrical pulses is performed using a Cliniporator (IGEA, Italy). It is possible to use a plate or needle electrode. Needle electrodes are of different shapes e.g. linear or hexagonal, with different lengths and spacing between pins. The Cliniporator generates 8 pulses with duration of 0,1 ms and 400 V at a frequency of 5 kHz with linear electrodes, and 4 pulses with duration of 0,1 ms and 730 V at a frequency of 5 kHz with hexagonal electrodes. The individual electrode is selected according to tumor size and localization. Cliniporator and electrodes are CE marked.

Anesthesia

The patients are anesthetized during treatment with local or general anesthesia. The anesthesia is planned in consultation between doctor and patient.

Biopsy

If the patient agrees biopsies will be performed from the tumor area before and after electroporation during local anaesthesia.

Patients with more than 6 metastases:

- One to two biopsies before treatment
- One to two biopsies one week after treatment from metastases treated with calcium and bleomycin respectively.

All patient's regardless number of metastases will have done one biopsy from area treated with calcium and one from area treated with bleomycin, after the randomization code is revealed.

All biopsies will be handled according to current guidelines and analyzed by a pathologist for amount of tumor tissue, inflammation, fibrosis and necrosis.

Duration

The treatment itself lasts a total of 30 to 60 minutes, depending if the patient receives local or general anesthesia. The patient will then be followed for up to 12 months with regular visits.

Stop Rules

The trial may be interrupted prematurely if:

- Treatment causes such severe side effects that a continuation of treatment is unacceptable
- Enrollment is too low to expect completion of the trial in its current form.

The Research Ethics Committee and the Medicines Agency will be informed about the end of the trial.

Statistical analysis

This is a randomized non-inferiority study comparing calcium electroporation with electrochemotherapy with intratumoral injection of bleomycin. For dimensioning tumor number, analysis of non-inferiority study is used. Tumor response is evaluated at each follow up with surveying. Documentation is done with digital color photography, including a ruler to estimate tumor size. Primary evaluation of the response will be based on criteria similar RECIST guidelines 1.1. Tumor response was analyzed using Fisher's exact test on objective response 6 months after treatment.

Response rate of tumors ≤ 3 cm treated with ECT with bleomycin is 85-100% (existing data). In this study, we have chosen not to put the expected response rate for ECT too high, but estimate it to 85%. We have no clinical results for the treatment of calcium electroporation, but on the basis of preclinical studies, the response rate for calcium electroporation is estimated to 70%. In order to detect a clinical difference in the two treatments of 15%, with a significant level of 0.1, and a power

of 80%, a minimum of 34 evaluable tumors need to be included. (Sample Size Calculator: https://www2.ccrb.cuhk.edu.hk/stat/proportion/tspp_sup.htm)

The metastases are evaluable 4 weeks after treatment. If a patient is excluded from the protocol before 4 weeks follow up, the patient will be replaced.

The number of patients that are being pulled out of the trial will be listed and primary reason for the exclusion will be described.