Phase III Randomized Double-blind Cross-over trial of Supersaturated Calcium-phosphate rinse (Caphosol®) versus NaCl 0.9% in the relief of Oral Mucositis in patients receiving Targeted Therapy

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To assess the effect of Caphosol® oral rinse on clinical outcomes of selected oral symptom burden (oral mucositis/stomatitis (aphthous-like), oral pain, taste change (dysgeusia), difficulty swallowing (dysphagia), difficulty oral intake, and dry...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON39444

Source
ToetsingOnline

Brief title
COMTT

Condition

- Miscellaneous and site unspecified neoplasms benign
- Skin appendage conditions

Synonym
oral disorders, oral mucositis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: EUSA Pharma

Intervention

Keyword: Caphosol, oral mucositis, oral rinses, targeted therapy

Outcome measures

Primary outcome

1. Assess the severity of patient-reported oral AEs as determined by the change in the VHNSS2.0(10) score 3 times a week, from onset of OM/S (aphthous-like), oral pain, taste change (dysgeusia), difficulty swallowing (dysphagia), difficulty oral intake, or dry mouth during the active oral rinse period with Caphosol® oral rinse versus NaCl 0.9% oral rinse, 4 times daily, 2 minutes with 30 ml solution

Secondary outcome

2. Determine the decrease in grade of OM/S (aphthous-like), oral pain, dysgeusia, dysphagia, and dry mouth, as measured by the NCI-CTCAE v4.0 once a week, during a 2 week treatment with Caphosol® oral rinse versus NaCl 0.9% oral rinse, 4 times daily, 2 minutes with 30 ml solution

3. Assess the incidence of dose delay or dose interruption, dose reduction and discontinue treatment owing to oral burden due to targeted anticancer therapy during the active oral rinse period, once a week

4. To correlate the incidence of oral mucositis with: grade >= 2 diarrhea, hand-foot skin reaction (HFSR), and papulopustular eruption (PPE) as measured by the NCI-CTCAE v4.0, during the active oral rinse period, once a week

5. Explorative analysis of polymorphism in MMPs and genes encoding for pharmacokinetic and pharmacodynamic variables related to the pharmacodynamics of the targeted anticancer agents

6. Prospectively explore the relationship between Herpesvirus excretion and the presence of oAEs in patients treated with TKI/mTORIs.

7. Investigate the histological features of OM/S and determine the tissue expression of matrix metalloproteinases (optional)

Study description

Background summary

Targeted therapies such as multi-targeted tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin inhibitors (mTORI) in renal cell carcinoma (RCC), demonstrate a high level of efficacy with acceptable tolerability. Currently, there are six EU approved targeted therapies available for treating RCC: sunitinib (Sutent®), sorafenib (Nexavar®), pazopanib (Votrient®), temsirolimus (Torisel®), everolimus (Afinitor®), and bevacizumab (Avastin®) plus interferon alfa-2-a. Because bevacizumab combined with interferon alfa-2-a has a different mechanism of action and side effect profile, patients with these agents will not be included.
Although some of these targeted therapies share a common mode of action, it should not be assumed that their adverse event (AE) profiles are similar. Indeed, evidence indicates clinically relevant differences between the toxicity profiles of targeted therapies - including between agents with similar mechanism of action. It should also be noted that the AE profile for a targeted agent may differ between tumor types.
Optimal antitumor activity requires maintaining the highest tolerable dose in individual patients. In order to improve health related quality of life (HRQoL) and patient adherence, adverse effects should be prevented, if possible avoided and treated if necessary. Current oral formulations consist of various schedules (continuous administration or 4 weeks on, 2 weeks off) to optimize the benefit-risk profile. Adherence to anti-cancer treatment is particularly important when prescribing oral therapies as adherence to the protocol can have a significant impact on efficacy and the severity of treatment-related AEs. As sorafenib, sunitinib, pazopanib, and everolimus are taken in the outpatient setting, patient education on the correct treatment dosing, usage and the nature, recognition, and severity of AEs is essential.

Since these agents have dermatological AEs in common, with oral mucositis/stomatitis (OM/S), hand-foot skin reaction (HFSR) and papulopustular eruption (PPE) as the most disabling AE, we require evidence based management options to prevent and treat these complications.
OM with mucosal change, associated pain, and taste change - are clinically relevant toxicities of TKI*s and mTORI*s presently in use. The incidence of OM/S of any grade is for sunitinib 38%, sorafenib 28%, pazopanib 4%, temsirolimus 41%, and for everolimus 44%.
An analysis of the appearance, clinical course, and toxicity profiles demonstrated that TKI and mTORI associated OM is distinct from conventional chemotherapy related OM, and more closely resembles aphthous stomatitis/aphthous like ulcerations. There is no consensus about the nomenclature yet, but in most studies these ulcerations are described as OM.
TKI/mTORI related OM/S may represent a dose-limiting toxicity for this new class of agents, especially considering the fact that even lower grades of OM/S with chronic daily dosing may be cumbersome to the patient and lead to dose reductions. Studies of management strategies may therefore be important for the dose adherence of TKI and mTORI and for the overall acceptance of this therapy for patients.
Recently, supersaturated calcium-phosphate rinse (Caphosol®), a Ca2+/PO43- mouth rinse, became available to prevent or treat OM. Caphosol rinse is registered on the basis that it met the medical need to manage clinical sequelae of OM in cytotoxic therapies. Caphosol is registered in the United States and in Europe as an adjunct to standard oral care in treating CM caused by radiation or (high-dose) chemotherapy. Relief of dryness of the oral mucosa in these conditions is associated with amelioration of pain. Caphosol has been shown to decrease the incidence, severity and duration of OM and pain and use of opioids of patients given a hematopoietic stem cell transplantation (HSCT).
The present multicenter randomized crossover study is aimed to assess the oral symptom burden (OM/S (aphthous-like), oral pain, taste change (dysgeusia), difficulty swallowing (dysphagia), difficulty oral intake, and dry mouth) originating from their targeted anticancer therapy, and to determine whether Caphosol® reduces these oral AEs.

Study objective

To assess the effect of Caphosol® oral rinse on clinical outcomes of selected oral symptom burden (oral mucositis/stomatitis (aphthous-like), oral pain, taste change (dysgeusia), difficulty swallowing (dysphagia), difficulty oral intake, and dry mouth) associated with incidence of grade >= 1 oral adverse events and the anticancer therapy cessation in patients treated with selected targeted anticancer therapy in selected tumors.

Study design

Multicenter, prospective, two-arm randomized, double blind, parallel-group,

cross-over design, phase III study

Intervention

The study will follow a cross-over design to maximize statistical power and decrease biases inherent to small samples as patients will become their own controls.
After a baseline assessment, patients will be randomly allocated to receive either Caphosol® or NaCl 0.9% rinse for the first rinse period (14 days). For rinse period 2 all patients will switch to the opposite treatment arm (NaCl 0.9% or Caphosol®).
The first 14 day oral rinse period will start within 2 days after the initial work-up. Because of the two week off treatment period within sunitinib treatment, this patients will start the oral rinse period between day 1-14 of a treatment cycle to last them a 14 day rinse period during active anticancer treatment. When selected AEs reappear, oral rinse period 2 will start. When selected adverse events are not resolved at the end of rinse period 1, patients start immediately with rinse period 2 without the wash-out period (sunitinib patients have to wait till start of next sunitinib cycle). During the wash out period patients rinse with self-prepared NaCl 0.9% rinse solution (one tea spoon of salt per 500 ml of water 4 times a day).
Duration and severity of OM/S (aphthous-like), oral pain, difficulty swallowing (dysphagia), difficulty oral intake, dry mouth, taste change (dysgeusia), changes in saliva consistency, and talking problems will be recorded three times a week by the patient and assessed weekly by the oncology staff.
Patients will be stratified by targeted anticancer agent and per tumor type in pre-defined cohorts.
A DNA blood sample will be taken at baseline for exploratory analysis of polymorphisms in Matrix metalloproteinases (MMPs) and in genes encoding for pharmacokinetic and pharmacodynamic variables related to the targeted anticancer agents.

Study burden and risks

The burden is to fill out 14 times a questionnaire (10 minutes each time) and optional a biopsy of the ulcer.

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

*Male and female subjects
* >=18 years of age
* Histological proof of cancer of any type
* Oral adverse events > grade 0 due to sunitinib, sorafenib, pazopanib, temsirolimus, or everolimus in mono therapy at study entry
* Written informed consent
* Eastern Co-operative Oncology Group (ECOG) performance status <= 2
* Able to perform oral rinsing
* Able to complete questionnaires by themselves or with assistance

Exclusion criteria

* Any previous systemic antineoplastic treatment within 4 weeks of initiation of current targeted anticancer therapy
* Current antineoplastic combination cytotoxic chemotherapy
* Physiologic condition that precludes the use of an oral rinse
* Hypersensitivity to Caphosol ingredients
* Use of palifermin, oral cryotherapy, low level laser therapy, topical oral steroids within 3 weeks of current targeted anticancer therapy

* Oral abnormalities defined as baseline oral assessment of NCI-CTCAE v4.0 grade > 0
* Current use of agents that are known to be strong inducers or inhibitors of CYP3A4 that can not be stopped

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-11-2011
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caphosol
Generic name:	supersaturated Calcium-phosphate rinse
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NaCl 0.9% (Sodium Chloride 0.9 %)
Generic name:	NaCl 0.9% (Sodium Chloride 0.9 %)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-01-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-03-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-02-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-12-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-09-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-10-2013

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2010-024425-20-NL
ClinicalTrials.gov	NCT01265810
CCMO	NL35073.058.11