Mass balance Study of Plitidepsin Administered Intravenously Over 3 Hours to Patients with Advanced Cancer

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The present study is aimed at identifying the specific routes of plitidepsin excretion and elimination following its administration to patients with advanced tumors. Also, the study design may allow the identification and quantification, if possible...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON42098

Source
ToetsingOnline

Brief title
APL-A-013-13

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer, cancer

Research involving
Human

Sponsors and support

Primary sponsor: PharmaMar
Source(s) of monetary or material Support: Pharma Mar

Intervention

Keyword: advanced cancer, plitidepsin

Outcome measures

Primary outcome

• To obtain the mass balance of plitidepsin in adult patients with advanced cancer.

• To identify the metabolites of plitidepsin formed in adult patients with advanced cancer.

Secondary outcome

• To determine, if possible, the concentration of as many plitidepsin metabolites as feasible in body fluids.

• To assess, if possible, whether cytochrome P450 (CYP) and/or UDP glucoronosyltransferase (UGT) enzyme genotypes, responsible for the metabolism of plitidepsin, are related to major differences in the availability of plitidepsin.

• To characterize the safety profile and feasibility of plitidepsin in patients with advanced cancer.

Study description

Background summary

This is an open-label, non-randomized, pharmacological study to characterize the mass balance of plitidepsin administered as a 3-hour (h) intravenous (i.v.) infusion fortnightly (Day [D] 1 and D15) every four weeks (q4wk). The first administered dose of plitidepsin will be radiolabeled with 14C; additional doses of plitidepsin will not be radiolabeled. Plitidepsin will be administered to six evaluable patients for a maximum of six cycles or until disease

progression (PD), unacceptable toxicity, consent withdrawal or while it is considered to be in their best interest.

Study objective

The present study is aimed at identifying the specific routes of plitidepsin excretion and elimination following its administration to patients with advanced tumors. Also, the study design may allow the identification and quantification, if possible, of any potential plitidepsin-related metabolite formed in patients with advanced tumors.

Study design

A total of six evaluable patients are expected to be treated with at least one plitidepsin infusion.
Patients will receive the study medication(s) for a maximum of six cycles and while it is considered to be in their best interest. Specifically, treatment will continue for a maximum of six cycles or until:
• PD.
• Unacceptable toxicity.
• Inter-current illness of sufficient magnitude to preclude safe continuation of the study.
• Patient*s refusal and/or non-compliance with study requirements.
• A protocol deviation with an effect on the risk/benefit ratio of the clinical trial.
• Dose omissions >= 2 plitidepsin infusions due to AEs related to plitidepsin.

Intervention

A total of six evaluable patients are expected to be treated with at least one plitidepsin infusion.
Patients will receive the study medication(s) for a maximum of six cycles
For the first cycle radiolabeled plitidepsin will be administered.

Study burden and risks

Everyone taking part in the study may have side effects and will be carefully watched. However, doctors do not know all side effects that may happen. Not all patients will experience them and they may be mild or very serious. Many of them will resolve soon after the patient will stop taking Aplidin®. In some cases, they can be serious, long lasting, or may not resolve. There is also a very small risk of death.

Based on experience from previous clinical trials, the occurrence of several side effects related to Aplidin® have been observed, usually moderate in intensity and reversible:

Likely (observed in >= 10% of patients):
* The most important side effect of Aplidin® concerns the muscles. It consists either of several short periods of muscular cramps or long-lasting muscular pain, mostly over shoulders and hips. Usually, these effects are not severe and do not need any treatment. Sometimes, it can be associated with muscular weakness and/or changes in blood tests (indicating muscular damage) that, exceptionally, can be severe. After stopping Aplidin® infusions, these effects usually resolve within two to three weeks.
* It is also very common to have some degree of transient fatigue, loss of appetite (anorexia), nausea and vomiting, diarrhea, and changes in blood tests related to liver function (blood transaminases, indicating liver damage). Usually they do not cause any symptom and resolve completely.

Common (observed in >=1% but in less than 10% of patients):
* Aplidin® injections tend to produce local irritation when administered into a blood vessel in the arm or hand. Therefore, infusion into a larger vein through a small subcutaneous venous access device that is permanently implanted is better; this procedure consists of minor surgery, usually with local anesthesia. This catheter is widely used in patients receiving other types of chemotherapy. The risks of a subcutaneous port are infection, clots and, rarely, kinks or rupture; if the needle is not properly inserted, fluids can leak into the tissue around the port. Occasionally, acute local pain over the catheter area appears during the administration of Aplidin®, or shortly afterwards. If your doctors should consider that a permanent catheter is not appropriate for you, it will be possible to infuse Aplidin® through a vein in the arm or hand, using a higher volume of fluids for diluting the drug, as it has been recently demonstrated that the frequency of complications between both infusion types (catheter versus peripheral vein) is not significantly different.
* Allergic reactions consisting of fever, shivering, skin rash and even difficulty to breathe may occur. Severe reactions have been observed in less than 5% of the patients treated to date. If severe allergic reactions occur, you will not be able to receive any further infusions of Aplidin®.
* Occasionally, some patients may have gastrointestinal disturbances, such as constipation, heartburn, inflammation of the mouth, abdominal pain, and taste disturbances.

Rare (observed in less than 1% of patients) but potentially serious:
* Severe effects on the blood cells are uncommon. Mild decreases in the number of white blood cells and platelets have been observed. However, there is always a possibility of having a severe decrease in the number of all blood cells, which can make you more vulnerable to have infections or bleeding.
* Other events that have been less frequently observed in patients in whom Aplidin® was administered are: changes in the levels of glucose in the blood, renal function impairment, cardiac impairment (mainly arrhythmia, palpitations and pulse acceleration), and blood clots in veins or lung embolism. Very infrequently (less than 1% of patients), Aplidin® may induce irreversible toxicities that may eventually have a fatal outcome.

Reproductive risks: Because the effects of Aplidin® during pregnancy have never been addressed formally in animals or in humans, we cannot exclude at this time whether its use may be harmful or deleterious in this situation. Therefore, the patient should not become pregnant or have a baby while participating in this study, and for at least six months after discontinuation of study treatment.
the patient should not nurse (breast-feed) a baby while on this study and also for six months after treatment discontinuation. Consequently, the patient and his/her partner must agree on using an effective contraception method to avoid pregnancy during the course of the study and for six months after discontinuation.
Should pregnancy of the female partner occur, she will be asked to sign a release of information form to allow the collection of information on the progress of the pregnancy and its outcome. The study doctor will make this information available to the Sponsor of the study for safety monitoring (follow-up).

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

1) Voluntarily signed and dated written informed consent (IC), obtained from the patient prior to any specific study procedure.
2) Patient*s availability to stay in the research unit up to a maximum of ten days.
3) Patients with histologically/cytologically confirmed diagnosis of advanced cancer (i.e., solid tumors, lymphomas and multiple myelomas) refractory to standard therapy or for whom no standard therapy exists or patients who have refused standard therapy.
4) Age >= 18 years.
5) Body Surface Area (BSA) >= 1.4 m^2.
6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score < 2.
7) Adequate bone marrow, renal, hepatic, and metabolic function (assessed <= 7 days before inclusion in the study):
a) Platelet count >= 100 x 109/L, hemoglobin >= 5.58 mmol/L and absolute neutrophil count (ANC) >= 1.0 x 109/L.
b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 3 x the upper limit of normal (ULN).
c) Total bilirubin <= 1.0 x ULN or direct bilirubin <= 1.0 x ULN when total bilirubin is above the ULN.
d) Calculated creatinine clearance (CrCl) >= 45 mL/minute (by means of Cockcroft and Gault*s formula).
e) Creatine phosphokinase (CPK) <= 2.5 x ULN.
f) Albumin >= 30 g/L.
8) Recovery to grade <= 1 from any adverse event (AE) derived from previous treatment (excluding alopecia of any grade and peripheral neuropathy grade <= 2).
9) Left ventricular ejection fraction (LVEF), by echocardiogram (ECHO) or multiple-gated acquisitions (MUGA) >= 50%.
10) Women of childbearing potential must have a negative serum pregnancy test before study entry. Both men and women must agree to use a medically acceptable method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception include: intrauterine contraceptive device (IUD), oral contraceptives, subdermal implant and double barrier (condom with a contraceptive sponge or contraceptive suppository).

Exclusion criteria

1) Concomitant diseases/conditions:
a) History or presence of unstable angina, myocardial infarction, valvular heart disease or congestive heart failure within the last 12 months.
b) Symptomatic arrhythmia or any arrhythmia requiring ongoing treatment, and/or prolonged QT-QTc grade>= 2.
c) Active uncontrolled infection.

d) Myopathy or any clinical situation that causes significant and persistent elevation of CPK (> 2.5 x ULN in two different determinations performed one week apart).
e) Limitation of the patient*s ability to comply with the treatment or follow-up protocol.
f) Any other major illness that, in the Investigator*s judgment, will substantially increase the risk associated with the patient*s participation in this study.
2) Symptomatic, progressive or corticosteroid-requiring documented brain metastases or leptomeningeal disease. Controlled and stable brain metastases without steroids are allowed.
3) Patients diagnosed with CNS tumors or leukemia.
4) Women who are pregnant or breast-feeding.
5) High transfusion requirements (> 2 packages of red blood cells and/or 1 platelet transfusion) in the 30 days prior to inclusion in the study.
6) Chemotherapy, radiotherapy, immunotherapy, or molecular targeted cancer therapy within the previous four weeks of the given drug, prior to the start of trial medication or concomitantly within this trial. This restriction does not apply to steroids and bisphosphonates.
7) Major surgical procedure within the last eight weeks prior to the start of trial medication.
8) Clinically relevant non-malignant disease, which in the Investigator's opinion would exclude the subject from the trial, such as significant cardiovascular, pulmonary, endocrine, renal and neurological disease or psychiatric disorder.
9) Known hypersensitivity to any of the excipients used.
10) Participation in another clinical trial or concomitant treatment with any investigational product in the 30-day period prior to inclusion in the study and/or participation in a 14C study within the last six months prior to screening for the current study. The total radioactivity exposure from the current study and the previous 14C study must be less than 5 mSv.
11) Tumoral or other conditions affecting the gastrointestinal tract or close to the gastrointestinal tract that may be expected to induce total or partial occlusion of the gastrointestinal transit.
12) Presence of, or history of, inflammatory bowel disease or digestive tract fistulae.
13) Significant constipation (defined as <1 deposition every 2 days or need for laxatives)
14) Any condition resulting in clinically evident obstruction of the urinary tract.
15) A history or regular use of tobacco- or nicotine-containing products within three months prior to screening.
16) Consumption of red wine, Seville oranges, grapefruit or grapefruit juice from two days prior to the first dose of study medication.
17) History of alcoholism.
18) Any condition that could interfere with the accurate assessment and recovery of radiocarbon [14C].
19) Unwillingness or inability to follow the procedures outlined in the protocol.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-03-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aplidin
Generic name:	Plitidepsin
Product type:	Medicine
Brand name:	radiolabeled Aplidin
Generic name:	radiolabeled 14C1-plitidepsin

Ethics review

Approved WMO Date:	04-11-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-02-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-03-2015

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2013-005011-26-NL
CCMO	NL49614.031.14