An Open-Label Phase I/IIa Study of the Safety and Efficacy of Melphalan-flufenamide (Melflufen) and Dexamethasone Combination for Patients with Relapsed and/or Relapsed-Refractory Multiple Myeloma

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Primary Objective(s)Phase I (completed)The primary objective of the Phase I portion of the study is to determine the maximum tolerated dose (MTD) of the combination of melflufen and dexamethasone in patients with relapsed/refractory multiple myeloma...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON47533

Source
ToetsingOnline

Brief title
O-12-M1

Condition

- Plasma cell neoplasms

Synonym
Multiple Myeloma / Kahler's disease

Research involving

Human

Sponsors and support

Primary sponsor: Oncopeptides AB
Source(s) of monetary or material Support: Oncopeptides AB

Intervention

Keyword: Melphalan-flufenamide and Dexamethasone Combination, Phase I/IIa, Relapsed / Refractory Multiple Myeloma

Outcome measures

Primary outcome

Primary Endpoint(s)

Phase I

The primary end point of Phase I is to determine the MTD by monitoring and

analyzing the frequency and grade of adverse events occurring at each dose

level of melflufen and dexamethasone to be tested.

Phase IIa

The primary end point of phase IIa is the objective response rate (CR, sCR,

VGPR, PR) and clinical benefit (* MR), in patients treated at the MTD.

Secondary outcome

Secondary Endpoint(s)

The overall response rate (CR/sCR, VGPR, PR) and clinical benefit (* MR), time

to progression, duration of response, progression free and overall survival in

all evaluable patients.

To further evaluate the frequency and grade of all adverse events of the

combination including the rate and type of second primary malignancies.

Study description

Background summary

In vitro studies demonstrate that melflufen provides better intracellular penetration of melphalan and therefore higher concentrations are achieved in tumors. In preclinical animal studies melflufen shows equimolar bone marrow toxicity profile to melphalan with better tumor growth suppression and has a strong antiangiogenic effect. The phase I-II trial conducted in advanced cancer patients has established the RPTD (recommended phase II dose) of melflufen to be 50 mg, at least in previously treated patients every 3 weeks with an acceptable safety profile. Melphalan is currently used clinically in multiple myeloma (MM). Cell culture studies demonstrate a greater cytotoxic potency of melflufen versus melphalan against MM cells without significant toxicity in normal cells. Overall, these preclinical and clinical studies provide the rationale for clinical protocols evaluating melflufen in multiple myeloma.

Study objective

Primary Objective(s)
Phase I (completed)
The primary objective of the Phase I portion of the study is to determine the maximum tolerated dose (MTD) of the combination of melflufen and dexamethasone in patients with relapsed/refractory multiple myeloma (MM).

Phase IIa
To evaluate the objective response rate * Partial Response (PR) and the clinical benefit (including minimal response [MR]) to the combination of melflufen and dexamethasone and melflufen as single agent at the MTD determined in Phase I.

Secondary Objective(s)
To evaluate the overall response including the complete response/stringent complete response (CR/sCR) and very good partial response (VGPR), partial response (PR) and clinical benefit (* MR), the time to progression, duration of response, progression free survival and overall survival in all evaluable patients.

To further explore the safety and tolerability of the combination at the MTD.
Exploratory Objective(s)
To identify mechanisms of response/resistance to melflufen.

Collection of bone marrow for whole-genome analysis is optional.

Study design

This is an open-label, phase I/IIa, multicenter study which will enroll patients with relapsed and relapsed/refractory multiple myeloma. Phase I will follow the standard 3 + 3 modified Fibonacci design with 3 to 6 patients, depending on dose limiting toxicity (DLT) observed, at each dose level to be tested. Up to 5 dose levels will be tested; IV melflufen at 15mg, 25mg, 40mg, 55mg and 70mg, given on day 1, in combination with a fixed dose of dexamethasone 40mg PO on days 1, 8 and 15 of each 28 day cycle.

Once the maximum tolerated dose (MTD) has been determined in Phase I, an additional 20 patients will be enrolled and treated at the MTD in the Phase IIa part of the study.

Patients will be assessed for response after each cycle according to the IMWG response criteria. Patients may receive up to 8 cycles of therapy. However, patients who have benefit from the therapy may continue treatment at the discretion of the investigator and after approval by the study sponsor for each individual case. Doses of melflufen or dexamethasone may be interrupted or reduced in an attempt to manage toxicity according to the protocol guidelines.

Intervention

The intervention concerns treatment with medicines (combination of melflufen/dexamethasone)

Study burden and risks

Treatment with the study drug may lead to the occurrence of unwanted symptoms. Side effects may be mild, severe or even result in death. Most side effects can be treated and resolve when treatment with the study drug is stopped, however, some side effects may be long lasting or permanent.

In the clinical studies conducted in patients so far, the most common (>10%) side effects observed for the study drug include leucopenia (low number of white blood cells), neutropenia (low number of neutrophils, a special type of white blood cell) and thrombocytopenia (low number of platelets). White blood cells form part of the immune system which helps to protect against infection and platelets are important in blood clotting. Fatigue (tiredness), nausea, occasional vomiting, diarrhea, irritation to the lining of the mouth and low red blood cell count have also been observed as side effects of the study drug. Red blood cells play an important role in your health by carrying fresh oxygen throughout the body and removing carbon dioxide. Irritation to the vein or site of administration may occur. The use of the infusion device will minimize this

risk. There is a low risk of a hypersensitivity reaction (allergic reaction). An allergic reaction may cause symptoms such as rash, difficulty breathing, drop in blood pressure and if severe, could be life threatening. You may experience none, some or all of those side effects listed here. There is always a risk of unknown side effects involved in taking a new drug but every precaution will be taken and you are encouraged to report anything that is troubling you. Melphalan has been known to increase the risk of developing secondary cancers. This risk is small but may also be associated with the study drug, melflufen.
Some common side effects observed for dexamethasone include weight gain, mood swings, acne and upset stomach. The side effects tend to go away if the dose is lowered or treatment is stopped. Other side effects of dexamethasone include infections, fluid retention (causing your body to hold onto excess fluid), gastrointestinal problems (irritation of the stomach and digestive tract, which can be reduced by taking antacids and by not taking your medication on an empty stomach) and high blood sugar.

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. Male or female, age 18 years or older.;2. Patient has a diagnosis of multiple myeloma with documented relapsed and/or relapsed-refractory disease.;3. Patient has measurable disease defined as any of the following:
* Serum monoclonal protein > 0.5 g/dL by protein electrophoresis.
* >200 mg of monoclonal protein in the urine on 24-hour electrophoresis
* Serum immunoglobulin free light chain >10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.
* If no monoclonal protein is detected (non-secretory disease), then > 30% monoclonal bone marrow plasma cells.;4. Patient has had at least 2 or more prior lines of therapy including lenalidomide and bortezomib and has demonstrated disease progression on or within 60 days of completion of the last therapy. (see appendix D for the definition of lines of therapy);;5. Life expectancy of *6 months;;6. Patient has an ECOG performance status * 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma will be eligible);;7. Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test prior to initiation of therapy;;8. Female patients of child bearing potential and non-vasectomized male patients agree to practice appropriate methods of birth control;;9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information;;10. The patient has or, accepts to have, an acceptable infusion device for infusion of melflufen (Port A Cath, PICC line or central venous catheter);;11. 12 lead ECG with QTcF interval of *470 msec;;12. The following laboratory results must be met within 21 days, or as specified in the table of assessments, prior to initiation of therapy:
* Absolute neutrophil count (ANC) * 1,000 cells/dL (1.0 x 109/L) (Growth factors cannot be used within 14 days before initiation of therapy).
* Platelet count * 75,000 cells/dL (75 x 109/L) (platelet count * 50,000 cells/dL for patients in whom * 50% of bone marrow nucleated cells are plasma cells (without transfusion during the previous 7 days to initiation of therapy).
* Hemoglobin * 8.0 g/dl (RBC transfusions are permitted)
* Total Bilirubin * 1.5 X upper limit of normal (ULN);
* Renal function: Estimated creatinine clearance * 45 ml/min or serum creatinine * 2.5 mg/dL;
* AST (SGOT) and ALT (SGPT) * 3.0 x ULN.
* (FCBP) is any sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months.

Exclusion criteria

1. Patient has evidence of mucosal or internal bleeding and/or is platelet transfusion refractory (i.e., unable to maintain a platelet count *50,000 cells/mm3);;2. Any medical conditions that, in the Investigator*s opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, * grade 3 thromboembolic event in the last 6 months), renal insufficiency (unless felt to be secondary to MM);;3. Known active infection requiring parenteral or oral anti-infective treatment;;4. Other malignancy within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix;;5. Other ongoing anti-myeloma therapy. Patients may be receiving concomitant therapy with bisphosphonates and low dose corticosteroids (e.g., prednisone up to but no more than 10 mg PO q.d. or its equivalent) for symptom management and comorbid conditions. Doses of corticosteroid should be stable for at least 7 days prior to initiation of therapy;;6. Pregnant or breast-feeding females;;7. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation;;8. Known HIV or hepatitis B or C viral infection;;9. Patient has concurrent symptomatic amyloidosis or plasma cell leukemia;;10. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes);;11. Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy. Biologic, novel therapy (including investigational agents in this class) or corticosteroids within 2 weeks prior to initiation of therapy. Patient has side effects of the previous therapy > grade 1 or previous baseline.;12. Prior peripheral stem cell transplant within 12 weeks of initiation of therapy*;;13. Radiotherapy within 21 days prior to initiation of therapy. However, if the radiation portal covered * 5% of the bone marrow reserve, the patient may be enrolled irrespective of he end date of radiotherapy;
14. Known intolerance to steroid therapy.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-09-2013

Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Melflufen (L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl)
Generic name:	Melflufen (L-melphalanyl-p-L-fluorophenylalanine ethyl ester HCl)

Ethics review

Approved WMO Date:	25-02-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	06-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2019
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-004315-31-NL
CCMO	NL43016.078.13