Clofarabine in combination with a standard remission induction regimen (AraC and idarubicin) in patients 18-60 years old with previously untreated intermediate and bad risk acute myelogenous leukemia (AML) or high risk myelodysplasie (MDS): a phase I-II study of the EORTC-LG and GIMEMA (AML-14A trial)

Published: 08-08-2007
Last updated: 11-05-2024

This is a phase I/II trial of the EORTC Leukemia Group and the italian GIMEMA Acute Leukemia Working Party. In a phase I setting we will investigate the optimal dosage and route of administration (one hour infusion or intravenous injection) of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON38148

Source
ToetsingOnline

Brief title
Clofarabine in patients with untreated AML/MDS

Condition

- Leukaemias

Synonym
acute myeloid leukemia

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: Genzyme Europe B.V.

Intervention

Keyword: Adult AML, Clofarabine, High risk myelodysplasie, Phase I-II study

Outcome measures

Primary outcome

Phase I study:

Safety and tolerability of clofarabine in combination with standard remission induction treatment for AML/MDS in order to determine the optimal dose for administration in the phase II trial

Phase II;

The efficacy (complete remission rate) after the remission induction course.

Secondary outcome

Phase I:

Efficacy (complete remission rate) after one or two remission induction courses and after the consolidation course, and hematopoietic recovery after the remission induction and after the consolidation course.

Phase II:

Safety/tolerability and activity expressed as complete remission rate after the consolidation course, hematopoietic recovery after the induction and consolidation courses, feasibility of the CD34+ cells harvest after the consolidation course. Diseasefree survival and survival after achievement of a complete remission, and overall survival.

Study description

Background summary

Patients with adult acute myeloid leukemia (AML) or high risk MDS are treated in specialized hospitals by the combination of high dose cytostatic agents such as cytosine arabinoside and anthracyclines with the aim to induce a remission of the disease.
A complete remission can be achieved in approximately 75% of patients under the age of 61 years. A consolidation course and a bone marrow transplantation are given in order to diminish the chance of relapse of the disease.
However, only 50% of the patients who reached a complete remission with survive for a long time without a relapse of the leukemia/MDS.
New antileukemic agents and/or treatment modalities are needed to further improve the prognosis of patients with AML.
Clofarabine is a new agent that, used as single drug in older patients, has shown a remarkable antileukemic activity. Little is known about its interactions with other established antileukemic agents with respect to activitiy and toxicity.

Study objective

This is a phase I/II trial of the EORTC Leukemia Group and the italian GIMEMA Acute Leukemia Working Party. In a phase I setting we will investigate the optimal dosage and route of administration (one hour infusion or intravenous injection) of clofarabine in combination with cytosine arabinoside and idarubicine. The selected dose/route of administration, based primarily on the toxicity profile, will be used in the subsequent phase II trial.
The aim of the phase II trial is to investigate the anti-tumor activity of the chosen dose and route of administration of clofarabine.

Study design

This is an open label, multicenter clinical trial with a sequential phase I/II

design.
The phase I part contains a dose-finding study with a classical phase I design using the 3+3 scheme aimed at documenting the safety profile and recommended dose of clofarabine in combination with standard AML treatment consisting of cytosine arabinoside and idarubicine.
Two different methods of administration (one hour infusion-Arm A or iv injection - Arm B) will be tested in parallel at a maximum of 5 different clofarabine dose levels.
The randomized phase II trial tests in parallel the 2 schemes (one hour infusion and intravous injection) at the maximal tolerated dose as found in the phase I trial. The Fleming 1-stage design will be applied for each arm.

Intervention

Remission induction course consisting of cytosine arabinoside, idarubicine and clofarabine:

Arm A: Clofarabine one hour infusion
Idarubicine 10 mg/m2 on days 1, 3 and 5
Cytosine arabinoside 100 mg/m2 cont. inf. on days 1 - 10
Clofarabine, test dose, on days 2, 4, 6, 8 and 10

Arm B: Clofarabine intravenous infusion
Idarubicine 10 mg/m2 on days 1, 3 and 5
Cytosine arabinoside 100 mg/m2 cont. inf. on days 1 - 10
Clofarabine, test dose, on days 2, 4, 6, 8 and 10

Test doses of clofarabine can be: 5, 7.5, 10, 15, 20, 25 or 30 mg/m2 per day

In case of treatment failure: patient off protocol
In case of partial remission: a second identical course can be given
In case of a complete remission (after one or two courses): a standard consolidation course (without clofarabine) followed by an autologous or allogeneic stem cell transplantation is strongly advised (but not part of the official protocol).

Study burden and risks

The most important activities of clofarabine are the induction of leukemic cell kill and of a longlasting pancytopenia. The most important side effects of clofarabine, as single agent, are transient liver and renal dysfunction and a number of less frequently occurring symptoms. These activities and side effects are not unique and occur frequently during and after standard treatment (containing cytosine arabinoside and idarubicine) of patients with acute leukemia. During this study effects and side effects will be observed very closely, and treated if possible, by the treating hematologist, and registered

on an almost daily basis at the EORTC Datacenter in Brussels. Groups of three patients will be evaluated by the Datacenter and the study coordinators, before a combination course with a higher level of clofarabine will start. With these measures we will minimize the risks for the patients as good as possible.
Phase II: Expectations on the efficacy of the new drug combination have been carefully described in the protocol. Each acute leukemia/MDS treatment is accompanied by a large number of severe side effects. The standard combination treatment together with the selected dose/ route of administration of clofarabine will be carefully evaluated by the EORTC Datacenter as well as the local hematologist in order to avoid a higher than expected number of severe side effects.

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Av. E. Mounierlaan 83/11
1200 Brussels
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Av. E. Mounierlaan 83/11
1200 Brussels
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age 20 * 60 years inclusive
WHO PS grade 0 * 2
previously untreated AML according to the new WHO criteria i.e. percentage bone marrow blasts > 20%
high risk MDS > 10% blast cells
All AML FAB subtypes except M3
All cytogenetic groups except those with the good risk features t(8;21), inv(16), and a WBC count at diagnosis of < 100 x 109/L
Written informed consent required

Exclusion criteria

Concomitant malignant disease
Central nervous system leukemia
Active uncontrolled infection
Inadequate renal function (creatinine > 2 mg/dl i.e. >= 2 x ULN) and liver function (bilirubin > 2 mg/dl, i.e. > 2 x ULN, ASAT/ALAT > 5 x ULN)
Concomitant severe uncontrolled cardiovascular disease i.e. symptomatic congestive heart failure or symptomatic ischemic heart disease
Any psychological, familial, sociological, and geographical condition potentially hampering compliance with the study protocol and follow-up schedule
Known HIV positivity
Pregnant (in case of doubt a pregnancy test is required) and breast feeding women

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-11-2008
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evoltra
Generic name:	clofarabine

Ethics review

Approved WMO Date:	08-08-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-05-2008
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	05-08-2008
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-09-2008
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	12-04-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-04-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-05-2012
Application type:	First submission
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	EUCTR2006-004912-28-NL
CCMO	NL18539.058.07