A Phase II randomized multicenter study to assess the efficacy of lenalidomide with or without erythropoietin and granulocyte-colony stimulating factor in patients with low and intermediate-1 risk myelodysplastic syndrome

Published: 20-02-2009
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Primary objective- To evaluate the efficacy of lenalidomide (RevlimidTM) in low/int-1 risk MDS with or without a treatment with Epo (NeoRecormonTM)/G-CSF (NeupogenTM) in terms of hematological improvement (HI) as defined by the modified response...

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

Summary

ID

NL-OMON47453

Source
ToetsingOnline

Brief title
HOVON 89 MDS

Condition

- Leukaemias

Synonym
MDS, myelodysplastic syndrome

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Celgene Corporation,Stichting HOVON;CKTO

Intervention

Keyword: erythropoetine, G-CSF, lenalidomide, MDS low and intermediate-1 risk

Outcome measures

Primary outcome

Primary endpoint

- Hematological improvement (HI) according to IWG 2006 criteria

Secondary outcome

Secondary endpoints

- Adverse events of CTCAE >= grade 2

- Time-to-HI and duration-of-HI (i.e. time from HI to relapse after HI or death from any cause)

- Number of given treatment cycles per patient, and especially for arm B the number of patients receiving Epo and/or G-CSF

- Response rate (in terms of CR, PR, including cytogenetic response according to the modified response criteria of the IWG for MDS

- Progression-free-survival, i.e. time from registration to relapse, disease progression or death from any cause

- Leukemic evolution. The risk of leukemic evolution will be calculated with competing risk death without previous evolution

- Number of transfusions of red blood cells and duration of RBC transfusion

independence

Study description

Background summary

In low/int-1 risk MDS no current standard treatment programs are available except for Epo/G-CSF in selected cases based on the predictive model of response to Epo/G-CSF (E. Helstrom-Lindberg; ELN 2008 recommendations; www.leukemia-net.org), in accordance with guidelines of several MDS working parties [23,26,27]. Based on new insights in the pathobiology of low/int-1 risk MDS new targets for therapy are emerging interfering with apoptosis of hematopoietic progenitors and interfering with the complex interactions of the microenvironment, the immune system and (leukemic)- progenitor cells. In this respect, lenalidomide with the pleiotropic effects including erythropoietic remitting activity in low/int-1 risk MDS is of particular interest. Epo/G-CSF might further potentiate the effects of lenalidomide by interfering with apoptotic signalling of hematopoietic precursor cells as well as with the optimisation of immune effector cell function. This might have impact on the survival of erythropoietic progenitor cells and their progeny with clinical and hematological improvement of patients with MDS. With respect to safety concerns, it is not likely that the addition of Epo/G-CSF to lenalidomide may induce an increased risk in hematological and/or non-hematological toxicities.

Study objective

Primary objective
- To evaluate the efficacy of lenalidomide (RevlimidTM) in low/int-1 risk MDS with or without a treatment with Epo (NeoRecormonTM)/G-CSF (NeupogenTM) in terms of hematological improvement (HI) as defined by the modified response criteria of the IWG for MDS

Secondary objectives
- To evaluate the safety and tolerability of lenalidomide (RevlimidTM) in low/int-1 risk MDS with or without Epo (NeoRecormonTM)/G-CSF (NeupogenTM)
- Time-to-HI and duration-of-HI
- Aantal gegeven kuren en aantal patienten dat Epo en/of G-CSF krijgt
- The number of given treatment cycles per patient and for arm B the number of patients receiving Epo and/or G-CSF
- The response rate (in terms of CR, PR, including cytogenetic response according to the modified response criteria of the IWG for MDS
- Progression-Free-Survival (i.e. time from registration to disease progression, including progression to leukemia, or death from any cause)

- Transfusion requirements of red blood cells

Study design

Phase II, multicenter, with randomisation between lenalidomide and lenalidomide + Epo/G-CSF in 200 patients with low or intermediate-1 risk myelodysplastic syndrome..

Intervention

For arm A: lenalidomide (Revlimid*) 10mg p.o./day 1-21 in a 28-day cycle. Patients will receive at least 6 cycles. If responsive, patients may continue treatment until loss of HI or progression of disease. For arm B: lenalidomide (Revlimid*)10mg p.o./day 1-21 in a 28-day cycle. After 4 cycles addition of erythropoietin (NeoRecormon*) s.c., 1x/wk 30000 to 60000IE depending on response. After 8 cycles, dependent on HI, G-CSF(Neupogen*) s.c, 3x/wk 300/480µg is added to according to current standard and validated treatment schedules. Patients will receive at least 12 cycles. If responsive, patients may continue treatment until loss of HI or disease progression.

Study burden and risks

No additional risks associated with participation of the study are yet known. To monitor either response or disease progression during therapy, every 3 month an additional bone marrow puncture is necessary. In general, this examination is not aggravating.

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

- Patients with MDS classified as:
* RA, RARS and RAEB (with <10% myeloid blasts), CMML (with <10% myeloid blasts), according to FAB or
*RA, RARS, RCMD, RCMD-RS, RAEB-1, MDS-U according to WHO or
*patients with MPD/MDS (CMML-1 according to WHO) with a WBC <= 12x109/l with an IPSS <= 1.0
- Hb <= 6.2 mmol/l (10.0 g/dl) or Hb <= 7.2 mmol/l and ANC <= 1.0x109/l or red blood cell transfusion dependent
- Age >= 18 years
- WHO performance status 0-2
- Patient not previously treated with Epo/G-CSF, or
failure of response or relapse after hematological improvement or disease progression to maximal RAEB-1 after previous therapy with Epo/G-CSF
- Serum creatinin < 150 µmol/l
- Serum billirubin < 25 µmol/l and ASAT, ALAT and Alkaline phosphatase < 2.5 times the upper limit of normal, except if related to disease
- The patient must give written informed consent
- Negative pregnancy test within 7 days prior to start of study drug, if applicable.
- Patient (all men, pre-menopausal women) agrees to use adequate contraceptive methods.
- Serum erythropoietin level
*> 200 U/l or
*<= 200 U/l if failure of response or loss of hematological improvement or disease progression to maximal RAEB-1 after prior standard therapy with Epo/G-CSF;
Epo/G-CSF should be stopped at least 1 month before randomization.

Exclusion criteria

- Severe cardiac, pulmonary, neurologic, metabolic or psychiatric diseases or active malignancies.
- Anemia due to other causes than MDS including iron, B12 and folate deficiencies, auto-immune hemolysis and/or paroxysmal noctural hemoglobinuria (PNH)
- Hypoplastic MDS
- High predictive score (score 0 or 1) to respond on standard treatment with Epo/G-CSF according to guidelines
- Active uncontrolled infection
- Absolute neutrophil count (ANC) < 0.5x109/l
- Patients dependent on platelet transfusions or with platelet counts < 25x109/l or patients with active bleeding
- Patients treated with biological response modifiers (i.e. growth factors, immunosuppressive agents and/or chemotherapy) within 1 month prior to randomization
- Lactating women
- Prior treatment with lenalidomide
- Prior CTCAE >= grade 3 allergic reaction/hypersensitivity to thalidomide
- Prior CTCAE >= grade 3 rash/blistering while taking thalidomide
- Prior CTCAE >= grade 3 allergic/hypersensitivity to Epo and/or G-CSF

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-05-2009
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NeoRecormon
Generic name:	Epoetine beta
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Neupogen
Generic name:	Filgrastim
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Revlimid
Generic name:	Lenalidomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-02-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-05-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2010

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-05-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2008-002195-10-NL
CCMO	NL25632.029.08
Other	NTR1825 & LN_NN_2009_392