A randomized phase II study for the evaluation of T cell depleted non-myeloablative allogeneic stem cell transplantation followed by early consolidation with lenalidomide or lenalidomide combined with bortezomib and subsequent DLI for patients with multiple myeloma in progression or relapse following first line therapy

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Primary objective:Assesment of feasibility and toxicity of T cell depleted NMA Allo-SCT followed by lenalidomide or lenalidomide combined with bortezomib,and subsequent DLI; as treatment of relapsed multiple myeloma.Secondary objectives:To...

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

Summary

ID

NL-OMON36688

Source
ToetsingOnline

Brief title
HO108 MM

Condition

- Plasma cell neoplasms

Synonym
Kahlers disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: stichting HOVON;KWF

Intervention

Keyword: Allogeneic-SCT, Immune therapy, Multiple myeloma, Novel agents

Outcome measures

Primary outcome

Failure free duration (FFD) at 9 months post-transplant. Patients count as a failure (= event) at the earliest time point within 9 months after Allo-SCT at which any of the following events occurs:

- Onset of acute GvHD grade 3-4 without prior DLI;

- Onset of extensive chronic GvHD without prior DLI;

- Non-hematological toxicity CTCAE grade 4;

- Systemic therapy for uncontrolled myeloma other than the assigned study treatment of lenalidomide or lenalidomide/bortezomib and DLI

- Death not due to (progression of) MM, which is in fact TRM.

Patients without a failure within 9 months post Allo-SCT will be censored at 9 months, at the date of progression, or when they go off protocol treatment,

whichever comes first.

Secondary outcome

- Toxicity profile and compliance related to each treatment step and intervals between treatment steps (Allo-SCT, consolidation chemotherapy as well as pre-emptive DLI);

- Percentage of patients with a 1st pre-emptive DLI within 6-9 months from the date of Allo-SCT;

- Response, improvement of response and conversion to full donor chimerism during the separate treatment phases (i.e. from Allo-SCT until consolidation; from consolidation to DLI; and after DLI);

- CR rate

- Progression-free survival (PFS; i.e. time from registration until progression, relapse or death, whichever comes first);

- PFS from Allo-SCT;

- Overall survival (OS) measured from time of registration;

- OS from Allo-SCT;

- The poportion of patients that complete 1, 2 resp. 3 induction cycles;

- Quality of life as defined by the EORTC QLQ-C30 and QLQ-MY20.

Study description

Background summary

This study will explore the feasibility and efficacy of T-cell depleted NMA Allo-SCT, followed by early consolidation with lenalidomide with or without bortezomib and subsequent DLI in relapsed myeloma patients. Patients with relapsed or progressive disease after first line therapy have a poor prognosis.

This is illustrated by the median survival of only 19 months after relapse from thalidomide maintenance of patients who were included in the HOVON 50 study. T cell depleted NMA Allo-SCT will avoid the occurrence of acute and chronic GvHD and will make it possible to create a platform for subsequent immune therapy like pre-emptive donor lymphocyte infusion. Timely consolidation after T cell depletion however is necessary to avoid early relapse. As consolidation strategy we will use either the thalidomide analog lenalidomide (CC-5013) or lenalidomide combined with bortezomib. Lenalidomide as this drug has a low toxicity profile, is highly effective against myeloma and has strong immune modulating effects. Bortezomib once weekly, may increase the efficacy of lenalidomide while on the other hand it may temper undesirable excessive immune stimulatory effects of lenalidomide and helps to separate the GvM effect from GvHD.

Study objective

Primary objective:
Assesment of feasibility and toxicity of T cell depleted NMA Allo-SCT followed by lenalidomide or lenalidomide combined with bortezomib,and subsequent DLI; as treatment of relapsed multiple myeloma.

Secondary objectives:
To investigate the efficacy of this regimen in terms of complete remission rate, overall and progression free survival.
To evaluate the quality of life with these regimens.

Study design

Randomized phase II

Intervention

T cell depleted NMA Allo-SCT followed by 3 cycles of lenalidomide 10 mg/daily or lenalidomide 10 mg/daily combined with weekly bortezomib 1.3 mg/m2 and preemptive DLI. The conditioning of NMA Allo-SCT is performed with melphalan/fludarabine and in vitro and in
vivo T cell depletion with Alemtuzumab (for MUD in combination with ciclosporin).

Study burden and risks

Patients with relapsed multiple myeloma have a limited life expectancy. A potential benefit for these patients is Allo-SCT to induce prolonged remissions especially when this procedure is followed by early consolidation with novel antimyeloma agents and subsequent pre-emptive DLI that may enhance the Graft versus Myeloma effect. The risks associated with this procedure is an estimated

Treatment Related Mortality between 10-15 % that is associated with Allo-SCT and reduced quality of life due to acute and chronic GvHD.

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 multiple myeloma with a first relapse or progression after first line therapy;
- Relapsed or progressive patients have received reinduction therapy before entering this trial;
- At least PR after reinduction treatment;
- 18-65 years,inclusive
- HLA-identical sibling or unrelated donor completely matched (10/10) (excluding identical twins);
- WHO-performance status 0-2;

- Written informed consent

Exclusion criteria

- No previous Allo-SCT;
- Severe pulmonary dysfunction (CTCAE grade III-IV, see protocol appendix D);
- Severe neurological or psychiatric disease;
- Patients with neuropathy, CTC grade 3 or higher;
- Significant hepatic dysfunction (serum bilirubin or transaminases * 3 times upper limit of normal);
- Significant renal dysfunction (creatinine clearance < 30 ml/min after rehydration);
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, cancer, etc.);
- History of active malignancy during the past 5 years with the exception of basal carcinoma of
the skin or or carcinoma *in situ* of the cervix or breast;
- Patient known to be HIV-positive;
- Patients with brain disease with the exception of those patients whose brain disease has been treated with either radiotherapy or surgery and remains asymptomatic, with no active brain disease, as shown by CT scan or MRI, for at least 6 months;
- The development of erythema nodosum if characterized by a desquamating rash while taking
thalidomide, lenalidomide or borium;
- Pregnant or breast-feeding female patients. Negative pregnancy test at study is mandatory for female patients of childbearing potential;
- Not able and not willing to use adequate contraception during therapy;
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule;
- Severe cardiac dysfunction (NYHA classification II-IV, see protocol appendix E).

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):	15-09-2011
Enrollment:	110
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic
Product type:	Medicine
Brand name:	alemtuzumab
Generic name:	alemtuzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	bortezomib
Generic name:	bortezomib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	fludarabine
Generic name:	fludarabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	lenalidomide
Generic name:	lenalidomide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	melphalan
Generic name:	melphalan
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	16-09-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-05-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-02-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	20-08-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2010-018494-37-NL

Register	ID
CCMO	NL32525.000.10