The Carthadex trial.

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Replacing bortezomib by carfilzomib would associate effective proteasome inhibition with lack of neuropathy, thereby improving the proportion of patients who are able to complete the planned treatment and reducing the rate of serious adverse events...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25987

Bron
NTR

Verkorte titel
The Carthadex trial

Aandoening

Multiple myeloma

Ondersteuning

Primaire sponsor: Erasmus MC
Overige ondersteuning: Erasmus MC receives financial support from Onyx Pharmaceuticals for the execution of this investigator sponsored trial.

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Response (Complete response (CR), very good partial response (VGPR), overall response (OR)):
1. After induction prior to HDM/ASCT;

2. After HDM/ASCT prior to consolidation treatment;
3. At end of consolidation treatment.

Toelichting onderzoek

Achtergrond van het onderzoek

Background of the study:

Thalidomide and bortezomib combined with dexamethasone and a third agent (alkylating agent or anthracycline) are now recognized as the most active drugs for remission induction in transplant candidates. In elderly patients they are combined with Melphalan/Prednisone (MP) in first line treatment. Both drugs share the disadvantage of inducing peripheral polyneuropathy which is dose limiting in 50% of patients and leads to premature termination of treatment in 25%.
Replacing bortezomib by carfilzomib would associate effective proteasome inhibition with lack of neuropathy, thereby improving the proportion of patients who are able to complete the planned treatment and reducing the rate of serious adverse events, in particular polyneuropathy. In view of the recently reported high response rates with Bortezomib containing regimens (VD, VRD, VCD, VTD, PAD) prior and after high-dose therapy, a regimen with Carfilzomib combining less polyneuropathy with similar efficacy would be a likely candidate for standard induction in the future. Equally, such
regimen could be used for short consolidation treatment after high-dose therapy

Objective of the study:

To assess the feasibility and efficacy of Carfilzomib in combination with Thalidomide and Dexamethasone in a phase II trial.

Study design:

This trial will establish the feasibility and efficacy of Carfilzomib, in combination with Thalidomide and Dexamethasone as an induction therapy prior to therapy with High Dose Melphalan (HDM) and Autologous Stem Cell Transplantation (ASCT) in previously untreated patients with Multiple Myeloma. Stem cell harvest will be performed using high-dose Cyclophosphamide and standard G-CSF. In addition, the efficacy of a short (4 cycles) post-transplant consolidation schedule of Carfilzomib, in combination with lower dose Thalidomide and Dexamethasone will be investigated. The study will be conducted as a Phase II trial. Fifty patients will be included in the study cohort. Molecular (FISH) characterization and gene expression profiling of the myeloma tumor cells will be performed at inclusion. All patients

will be followed closely for toxicities and response assessment, as indicated. After completion of treatment, all patients will be followed two-monthly until relapse or progression.

Study population:

Patients with Multiple Myeloma, ISS stage II/III age 18-65 yrs (must be transplant candidates) at first presentation; 50 patients.

Intervention:

The treatment is composed of the standard therapy for patient with Multiple Myeloma at first presentation. Instead of giving, in the consolidation & induction phase, Thalidomide, Dexamethason and a third agent (i.e. Bortezomib), Carfilzomib will be administered in combination with Thalidomide and Dexamethasone.

Primary study parameters/outcome of the study:

To establish the response, in patients with Multiple Myeloma at first presentation, to carfilzomib in combination with thalidomide and dexamethasone.

Secundary study parameters/outcome of the study:

To investigate the clinical efficacy and toxicity of carfilzomib in combination with thalidomide and dexamethasone in remission induction of Multiple Myeloma at first presentation.

To investigate the clinical efficacy and toxicity of carfilzomib in combination with thalidomide and dexamethasone in consolidation treatment of Multiple Myeloma at first presentation.

To assess the stem cell harvest following carfilzomib in combination with thalidomide and dexamethasone. To assess Progression-free survival (PFS).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Carfilzomib has been given as monotherapy and also in combination with Lenalidomide and dexamethsone but not with this peticular antimyeloma standard chemotherapy regimen. So unexpected toxicites are possible.

A “first-dose” effect has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. At time of the normal bone marrow punctions a limited amount of extra bone marrow will be collected via the same needle.

Doel van het onderzoek

Replacing bortezomib by carfilzomib would associate effective proteasome inhibition with lack of neuropathy, thereby improving the proportion of patients who are able to complete the planned treatment and reducing the rate of serious adverse events, in particular polyneuropathy.

Onderzoeksopzet

1. induction treatment cycles;

2. High-dose Melphalan and autologous stem cell transplantation;

3. Consolidation cycles;

4. 2 monthly follow up.

Onderzoeksproduct en/of interventie

Induction cycles:

1. Carfilzomib 20/27mg/m2 days 1,2,8,9,15,16 of a 28 day cycle;

2. Thalidomide 200 mg days 1-28 of a 28 day cycle;

3. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle.
4. 4 cycles.

Stem Cell Harvest.

HDM 200mg/m2 ASCT.

Consolidation cycles:

1. Carfilzomib 27mg/m2 days 1,2,8,9,15,16 of a 28 day cycle;

2. Thalidomide 50 mg days 1-28 of a 28 day cycle;

3. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle;

4. 4 cycles.

Fifty patients will be included in the study cohort. Extensive molecular (FISH) characterization and gene expression profiling of the myeloma tumor cells will be performed at inclusion. All patients will be followed closely for toxicities and response assessment, as indicated. After completion of treatment, all patients will be followed two-monthly until relapse or progression.

For patient numbers 1 to 50

Induction treatment (before HDM/ASCT):

Carfilzomib 20mg/m2 for days 1,2, then 45mg/m2 days 8,9,15,16 of cycle 1, then 27mg/m2 throughout next cycles.

Thalidomide 200 mg days 1-28 of a 28 day cycle.

Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle.

4 cycles.

Consolidation treatment (guideline 8 weeks after HDM/ASCT):

Carfilzomib 27mg/m2 days 1,2,8,9,15,16 of a 28 day cycle.

Thalidomide 50 mg days 1-28 of a 28 day cycle.

Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle.
4 cycles.

For patient numbers 51 to 70

Induction treatment (before HDM/ASCT):

Carfilzomib 20mg/m2 for days 1,2, then 45mg/m2 days 8,9,15,16 of cycle 1, then 36mg/m2 throughout next cycles.

Thalidomide 200 mg days 1-28 of a 28 day cycle.

Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle.
4 cycles.

Consolidation treatment (guideline 8 weeks after HDM/ASCT):

Carfilzomib 36mg/m2 days 1,2,8,9,15,16 of a 28 day cycle.

Thalidomide 50 mg days 1-28 of a 28 day cycle.

Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle.
4 cycles.

Contactpersonen

Publiek

P.O. Box 2040
P. Sonneveld
Erasmus University Medical Center,
Department of Hematology
Rotterdam 3000 CA
The Netherlands
+31 (0)10 7033589

Wetenschappelijk

P.O. Box 2040
P. Sonneveld
Erasmus University Medical Center,
Department of Hematology
Rotterdam 3000 CA
The Netherlands
+31 (0)10 7033589

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Patients with a confirmed diagnosis of multiple myeloma stage I to III according to the ISS

criteria;

2. Age 18-65 years inclusive;

3. WHO performance status 0-3 (WHO=3 is allowed only when caused by MM and not by co-morbid conditions);

4. Negative urine pregnancy test at inclusion if applicable;

5. Written informed consent.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Known intolerance of Thalidomide;

2. Systemic AL amyloidosis;

3. Non-secretory MM;

4. Waldenstrom's macroglobulinemia or IgM MM;

5. Previous chemotherapy or radiotherapy except 2 cycles of Melphalan/Prednisone or local radiotherapy in case of local myeloma progression;

6. Severe cardiac dysfunction (NYHA classification II-IV, see appendix III);

7. Severe pulmonary dysfunction;

8. Significant hepatic dysfunction (serum bilirubin 30 mol/L or transaminases 3.0 times normal level), unless related to myeloma;

9. Creatinine clearance (measured or calculated) <15cc/min;

10. Alkaline Phosphatase >3x ULN;

11. ANC < 1,0 x109/L, platelets < 75 x109/L, Hb < 4.9 mmol/L;

12. Non-secretory MM defined as SPEP < 5 g/L and UPEP < 200 mg/24 hr;

13. Intolerance to thromboprophylaxis;

14. Patients known to be HIV-positive;

15. Patients with active, uncontrolled infections;

16. Patients with neuropathy, CTC grade 3 or higher, or grade 2 painful peripheral neuropathy;

17. Patients with a history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma;

18. Patients (all males and all pre-menopausal women) who are not willing or capable to use adequate contraception during the therapy;

19. Lactating women;

20. WHO Performance status > 3.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	26-07-2010
Aantal proefpersonen:	145
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	22-07-2010

Soort: Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2316
NTR-old	NTR2422
Ander register	METC Erasmus MC : 2010-029
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A