Non myeloablative allogeneic stem cell transplantation following high dose therapy as part of first line therapy to induce graft versus myeloma for patients ≤ 65 years participating in the HOVON 50 study.

PROTOCOL

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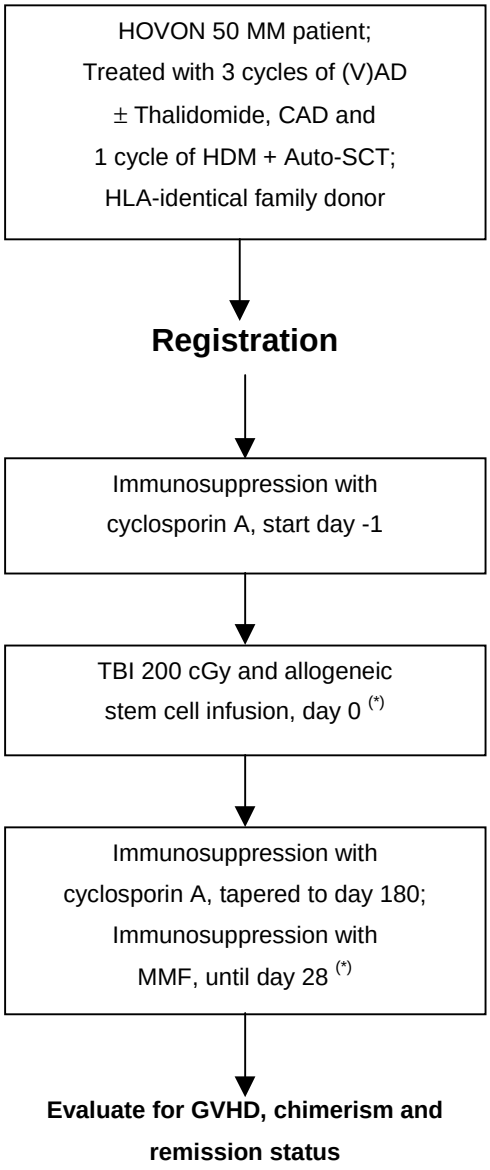
1 Scheme of study



(*) Note: patients who have received an allogeneic stem cell transplantation, will NOT receive maintenance therapy according to the HOVON 50 MM protocol

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3 Synopsis

Study phase	Phase II
Study objectives	Efficacy of non myeloablative Allo-SCT following intensive treatment including autologous stem cell transplantation
Patient population	Patients with multiple myeloma, with an HLA-identical family donor, participating in the HOVON 50 MM trial, who have received 3 cycles of (V)AD ± Thalidomide, CAD and 1 cycle of HDM + Auto-SCT
Study design	Prospective, multicenter
Duration of treatment	Expected duration of treatment is 6 months (TBI and transplantation 1 day, immunosuppression 6 months)
Number of patients	40 patients
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported
Planned start and end of recruitment	Start of recruitment: I 2003 End of recruitment: I 2006

4 Investigators and study administrative structure

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5 Introduction

5.1 Intensive treatment

High dose chemo-radiotherapy has improved response rate dramatically in Multiple Myeloma (MM). Especially when applied early in the course of the disease, myeloablative treatment followed by autologous stem cell rescue may induce responses in more than 80% of the patients including a considerable number of patients with a complete response (CR).[1-4] So far only one phase III trial has been published indicating that intensive treatment may also improve overall survival (OS) compared to conventional chemotherapy.[5] A better survival was also observed by the Nordic Study Group which compared patients treated with Melphalan 200 mg/m^2 with historical controls.[6] However it remains questionable whether chemo-radiotherapy alone can eradicate the clonogenic myeloma cell. There is no plateau in the progression free survival (PFS) and OS curves following Autologous Stem Cell Transplantation (Auto-SCT) and even patients in so-called CR continue to relapse. This is in accordance with the observation that molecular remissions after myeloablative therapy followed by Auto-SCT are rare.[7]

5.2 Graft versus myeloma and allogeneic stem cell transplantation

Recently the existence of a Graft versus Myeloma (GVM) effect was proven by the induction of remissions by Donor Lymphocyte Infusions (DLI) in patients with relapsed MM after Allogeneic Stem Cell Transplantation (Allo-SCT).[8,9] In a recent update of 27 patients, response to DLI was 52% and 30% of patients attained a CR. In 3 patients a molecular remission after DLI is now sustaining for more than 48 months, suggesting a curative potential of adoptive T-cell therapy in MM.[10]

The necessity of performing Allo-SCT in MM however is still disputed. Median OS in different reports varies from 18 to 28 months from transplantation.[11-16] A survival advantage for patients receiving an Allo-SCT compared to patients with the same characteristics treated with Auto-SCT and no SCT at all has not been shown. In a retrospective case-matched analysis performed by the European Bone Marrow Transplantation (EBMT) registry the OS of patients receiving Auto-SCT was significantly better than of Allo-SCT patients. Only for patients alive at 1 year post-transplant OS and EFS were prolonged after Allo-SCT.[17] A major reason for the poorer outcome of Allo-SCT is the high rate of Treatment Related Mortality (TRM, usually around 40%) which is not compensated for by a higher CR rate and lower relapse rate. An important factor responsible for the excessive toxicity of Allo-SCT in MM may be the high percentage of pretreated and refractory disease and the relatively high age of patients included in published studies.

Since 1991 two intensive treatment protocols for MM were performed in the Netherlands and in Belgium under auspicies of the Dutch-Belgian Haemato-Oncology Cooperative Group HOVON. In the recently closed phase III HOVON 24 MM trial with 453 patients, Interferon-α-2a (IFN) maintenance was compared to Auto-SCT and IFN maintenance following intensive induction therapy with Vincristine, Adriamycin, Dexamethasone (VAD)[18] and Intermediate Dose Melphalan (Melphalan 70 mg/m^2, IDM)[19]. Patients under 56 years with an HLA-identical sibling could be allocated to Allo-SCT after induction therapy. This approach was chosen in order to evaluate the efficacy of early Allo-SCT on TRM and its possible favourable effect on long-term outcome in comparison with patients that received intensive treatment with or without Auto-SCT.
Recent interim evaluation of the HOVON 24 study showed that 56 patients who were allocated to Allo-SCT had a significantly inferior outcome as compared to an age-matched group of 73 patients who were eligible after induction therapy for further treatment (IFN or Auto-PBSCT). Median OS after Allo-SCT was 25 months versus 47 months in the Auto-SCT/IFN group. A major reason for the inferior outcome of Allo-SCT was the high treatment related mortality of 32% which was not compensated for by a favourable graft versus myeloma effect. These results indicate that there is no indication for standard Allo-SCT as part of front-line therapy for myeloma.

5.3 Non myeloablative allogeneic hematopoietic stem cell transplantation

Non Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation (NMA Allo-SCT) has been explored extensively in recent years in a variety of hematological malignancies including multiple myeloma.[20-27] The objective of this approach is to lower transplant related mortality by reducing the intensity of the conditioning regimen while sparing the graft versus tumor effect of donor T-cells. Serious organ damage characteristic of conventional transplantation is prevented and avoiding profound pancytopenia reduces infection risks. Another advantage may be that minimally cytotoxic conditioning allows persistence of host antigen-presenting cells, thus enhancing presentation of host minor antigens to donor T-cells and initiation of graft versus tumor.
Sustained engraftment after NMA Allo-SCT is achieved by immunosuppressive (and myelosuppressive) chemotherapy, usually including purine analogs like Fludarabine and alkylating agents like cyclophosphamide or low dose Total-Body Irradiation (TBI), given before transplantation combined with vigorous postgrafting immunosuppression.[22,23,25]
The feasibilty and effectiveness of NMA Allo-SCT has been demonstrated in many studies, even in patients of older age (up to seventy years) and with heavily pretreated refractory disease. Treatment related mortality seems to be lower as compared to conventional Allo-SCT although the follow-up in most studies is too short to evaluate the long term effects on survival especially of chronic (extensive) Graft versus Host Disease (GVHD), which is a frequent complication of NMA Allo-SCT.[20-27]

Also in multiple myeloma several studies with NMA Allo-SCT have been performed. Badros reported on 31 patients who received allografts from HLA-matched siblings (n = 25) or unrelated donors (n = 6) using a mini-allograft following conditioning with Melphalan 100 mg/m^2.[28] Seventeen of these patients had progressive disease (PD) and 14 had responsive disease (RD). Thirty patients had received one (n = 13) or two or more (n = 17) prior autologous transplantations. At a median follow-up of 6 months, 19 (61%) of 31 patients achieved complete/near complete remission. So far 12 (39%) have died: three of PD, three of early TRM and six of late TRM. Median overall survival (OS) was 15 months. When compared with historical MM controls (n = 93) receiving conventional allografts, early TRM was significantly lower (10% v 29%, P =.03), and OS at 1 year was better (71% vs 45%; P =.08) in the mini-allograft MM patients. The authors conclude that mini-allograft induced excellent disease control in MM patients with high-risk disease, but is still associated with a significant GVHD.

The Seattle group has used a different strategy in MM patients. In their protocol patients are treated with high dose Melphalan 200 mg/m^2 and autologous stem cell rescue followed after 60 - 90 days by an Allo-SCT from HLA-identical sibs after minimal conditioning with low dose TBI, 200 cGy alone or combined with Fludarabine and post-transplant immunosuppression with cyclosporin A and mycophenolate mofetil.[29] By separating the high-dose conditioning regimen from the immunotherapeutic effect of the allograft, they hoped to decrease the TRM, yet provide the allogeneic effect of graft versus myeloma. Thirty-two patients with a median age of 55 (range 39-71) years, with previously treated stage II/III myeloma (43% refractory or relapsed disease) were included. All patients engrafted with medians of 90% of donor T-cell chimerism by day +28 after allografting and 99% by day +84, with no graft rejection. With median follow-ups of 423 days after autologous and 328 days after non-myeloablative Allo-SCT, overall survival is 81%. Day 100 mortality was 6% (one death after autologous and one from progressive disease after Allo-SCT). Forty-five percent of patients developed acute grade II-IV GVHD (II in all but 3 cases), and 55% developed chronic GVHD requiring therapy. The response rate was 84% with 53% CR and 31% PR and only two progressions to date. Six patients have died, one following the autograft due to CMV, five following the allograft due to disease progression (1), GVHD (2), encephalopathy (1), infection and chronic GVHD (1). The investigators conclude that despite being used in an older group of patients with multiple myeloma, this novel two-step allografting approach has dramatically reduced the acute toxicities of Allo-SCT while maintaining potent anti-tumor activity.

At the department of Haematology UMCU, Utrecht, the Netherlands, non myeloablative Allo-SCT following conditioning with low dose TBI/Fludarabine (+ATG in the non related transplants) using HLA-identical sibs (n=7) and unrelated donors (n=3) has been performed in 10 heavily pretreated patients including 4 MM patients. All patients engrafted rapidly and full donor chimerism was shown in all patients at day +28. One patient with relapsed acute lymphoblastic leukemia, who was treated with NMA from an unrelated donor 3 months after autologous stem cell transplantation,

died from TRM. In the remaining patients no excessive toxicity was recorded and acute and chronic GVHD were manageable. Anti-tumor effects were observed in 3 out of 4 myeloma patients, 1 of 2 ALL patients, 1 of 2 lymphoma patients and 1 of 1 CML patient. The follow-up period however is too short for conclusions about long term efficacy.

5.4 Rationale of the study

This is a phase II study to test the efficacy of non myeloablative Allo-SCT following high dose chemotherapy in HOVON 50 patients who received 3 cycles of (V)AD ± Thalidomide, CAD and 1 cycle of HDM followed by autologous stem cell infusion. The outcome of multiple myeloma has improved in the last decade by the application of intensive treatment protocols, however the disease can not be cured by chemo-radiotherapy alone and all patients die after initial response of multidrug resistant disease. This urges the further exploration of new strategies which are not solely based on the effect of chemo-radiotherapy alone.

Donor lymphocyte infusions given to patients with relapsed multiple myeloma after conventional Allo-SCT may induce sustained molecular remissions, indicating a curative potential of alloreactivity in MM. However due to the high TRM of conventional Allo-SCT, even when applied as part of first line treatment, there is no indication for myeloablative Allo-SCT as front line therapy. Non myeloablative Allo-SCT using HLA-identical related and non related donors has been used in hundreds of patients now with a wide variety of hematological and non hematological malignancies. Although the majority of these patients were not eligible for conventional Allo-SCT due to low performance, older age or refractory disease, impressive results were obtained in several patient groups showing the efficacy of a graft versus tumor effect after minimal conditioning at the cost of acceptable toxicity and TRM.

In multiple myeloma most promising results were obtained after effective tumor reduction by high dose chemotherapy and autologous stem cell rescue followed by minimal conditioning with low dose TBI ± Fludarabine and HLA-identical stem cell transplantation. A high CR rate was achieved by the Seattle group in patients who were not eligible for conventional Allo-SCT. Several other groups are exploring this approach and preliminary results confirm the efficacy and feasibility of combining an allogeneic graft versus myeloma effect with high dose therapy with autologous stem cell rescue.

6 Study objectives

- To assess the efficacy of non myeloablative allogeneic haematopoietic stem cell transplantation following intensive chemotherapy with respect to progression free survival
- To evaluate chimerism, response rate (especially complete response) and overall survival
- To evaluate TRM, acute and chronic GVHD

7 Study design

Details of all treatments (dose and schedule) are given in 9.1 - 9.9.

One day before the planned date of NMA Allo-SCT (day -1) immunosuppression with cyclosporin A will start. On day 0 TBI 200 cGy will be given, followed by unmodified G-CSF mobilized allogeneic stem cell infusion. Immunosuppression with cyclosporin A will continue until day 180, with additional MMF given until day 28.
Patients who have received an allogeneic SCT will NOT receive maintenance therapy according to the HOVON 50 MM protocol.

8 Study population

8.1 Eligibility for registration

All eligible patients have to be registered after evaluation of HDM + Auto-SCT and before start of immunosuppression for NMA Allo-SCT (see 16.1).

8.2 Patient selection

8.2.1 Inclusion criteria

- Age 18-65 years inclusive;
- Included in the HOVON 50 MM study;
- Patient has received 3 cycles of VAD or AD+Thalidomide, CAD and 1 cycle of high dose Melphalan with autologous stem cell reinfusion according to HOVON 50 MM protocol;
- NMA allogeneic transplantation planned between 2 and 6 months after autologous stem cell reinfusion;
- WHO performance status 0-2 (see appendix C);
- HLA-identical family donor;
- Written informed consent.

8.2.2 Exclusion criteria

- Creatinin clearance < 50 ml/min;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix D) ;
- Significant hepatic dysfunction (serum bilirubin ≥ 30 μmol/l or transaminases ≥ 2.5 times normal level), unless related to myeloma;
- Patients known to be HIV-positive;
- Patients with active, uncontrolled infections;
- Progressive disease / relapse from CR / progression from MR or PR after HDM with autologous stem cell reinfusion according to HOVON 50 MM protocol.

8.3 Donor selection

8.3.1 Inclusion criteria

- HLA genotypically identical sibling;
- Informed consent to undergo G-CSF administration and leukapheresis;
- Adequate veins for leukapheresis or agrees to placement of central venous catheter;
- Willing and able to undergo apheresis procedure according to institutional guidelines.

8.3.2 Exclusion criteria

- Monozygotic identical twin;
- Age less than 12 years;
- Pregnancy;
- Known allergy to G-CSF;
- HIV positive;
- Current serious systemic illness.

9 Treatments

9.1 Outline of treatment

In patients who enter the HOVON 50 study, the search for an HLA-identical sibling donor will be made as soon as the patient has decided to participate in the study. Patients who have an HLA-identical sibling donor are candidate for a non myeloablative transplant. The NMA Allo-SCT will be performed not earlier than 2 months and not later than 6 months following the autologous stem cell reinfusion after 1 cycle of HDM.

9.2 Conditioning regimen

Day 0: Total body irradiation 200 cGy followed by unmodified G-CSF mobilized allogeneic stem cell infusion. Because the dose is only 200 cGy, no protection or compensation is necessary.

9.3 Immunosuppression

Day -1: Start cyclosporin A at 6.25 mg/kg orally, twice daily to day +84 and taper to day +180. Tapering will be a ~8% dose reduction per week during 11 weeks, unless GVHD develops.
Day 0: Start mycophenolatel mofetil (MMF) at 15 mg/kg, orally twice daily to day +28. The first dose will be be given 5-10 hours after the allogeneic stem cell infusion.

9.4 Collection of donor PBSC

All donors will receive G-CSF 5 μg/kg, s.c. twice daily for 5 consecutive days from day -4 to day 0. The leukapheris procedure starts on day -1 and may be repeated on day 0.

9.5 PBSC infusion

At day 0 patients should receive unmodified donor PBSC containing at least 4 x 10^6/kg CD34+ cells.

9.6 Maintenance therapy

No maintenance therapy will be given after non myeloablative allogeneic transplantation like in the HOVON 50 study. Both Interferon-α and Thalidomide may influence the occurrence and/or severity of Graft versus Host disease.

9.7 Scheme of treament

Day number	-1	0	+1	+28	+29	+56	+84	+180
Cyclosporin A	START	→	→	→	→	→	TAPER[2]	STOP
TBI		200 cGy						
Stem cell infusion		Infusion						
MMF		START[1]	→	STOP				

[1]First dose of MMF will be given 5-10 hours after allogeneic stem cell infusion

[2]Tapering will be a ~8% dose reduction per week during 11 weeks, unless GVHD develops

9.8 Special management orders

9.8.1 Cyclosporin A

- Cyclosporin A is given at 6.25 mg/kg orally, twice daily from day -1 to day +84 and then tapered to zero at day +180 unless GVHD develops. As this high dosage is often accompanied by severe nausea and vomiting, especially in combination with the TBI, scheduled anti-emetic therapy is recommended for all patients for at least a week after transplant. Alternatively the cyclosporin can be given i.v. at a dose of 1.5 mg/kg. When dose adjustments are necessary it should be aimed at maintaining the blood levels in the upper part of the therapeutic range.
- Regular routine controls should include blood pressure, renal function, electrolytes and magnesium.
- Drugs that influence cyclosporin levels include: dilantin, phenobarbital, steroids, fluconazole, cimetidine.

9.8.2 Mycophenolate mofetil (MMF)

- MMF, 15 mg/kg, orally twice daily is prescribed from day 0 to day +28 and stopped without tapering. As MMF tablets are 500 mg, in practice most patients will receive 1000 mg MMF twice daily.
- Principle side effects include diarrhea, leukopenia, gastrointestinal bleeding and vomiting. In case of severe gastrointestinal toxicity, likely to be due to MMF, a 20% dose reduction is recommended and in case of no improvement a further 20% reduction. In extreme cases MMF can be temporarily stopped. Dose adjustments should not be made for hematopoietic toxicity unless severe neutropenia persists for more than 5 days.

9.8.3 Infection prophylaxis and CMV/EBV monitoring

Standard infection prophylaxis during neutropenia should be given according local protocols. Patients will receive prophylaxis for PCP and HSV for at least 1 year or longer in case of continued GVHD and/or immunosuppression. Oral valacyclovir, 3 dd 1 g, will start on day -1 and continued until day +21. Thereafter valacyclovir 2 dd 500 mg is prescribed. Standard EBV and CMV monitoring/prophylaxis should start at the time of transplant and should continue at least 90 days or longer on indication.

9.9 Treatment of progression / relapse

If there is relapse from CR or progression from PR/MR, it is recommended to reinduce with VAD (3 courses) followed by low dose DLI (1 x 10^7 T-cells/kg). If there is no response (and no active GVHD) measured 3 months after low dose DLI, this may be followed by high dose DLI (1 x 10^8 T-cells/kg). Patients with no response to reinduction therapy with VAD may be treated immediately with high dose DLI (1 x 10^8 T-cells/kg).

Mixed chimerism following NMA Allo-SCT is no indication for DLI.

9.10 Advised treatment of Graft versus Host Disease

Acute GVHD

Grade I localized to skin: corticosteroid ointment on affected sites.

Grade II-IV:

1. Prednisone 1 mg/kg/12 hours orally or methylprednisolone 1 mg/kg/12 hours for at least 10 days. In case of good response taper to zero in 3 weeks (Ganciclovir prophylaxis in CMV positive patients and strict EBV monitoring!);
2. In case of no response: methylprednisolone 30 mg/kg/12 hours for 5 days, and then follow scheme under (1);
3. In case of no response: resume MMF in case this was already stopped;
4. ATG as last option.

Chronic GVHD

Localized to skin: corticosteroid ointment.

Localized to oral cavity: consider to rinse with cyclosporin or corticoid solution.

Extensive GVHD:

1. Prednisone usually 0.5 - 1.0 mg/kg/day;
2. In case of resistant extensive chronic GVHD the following treatments may be initiated (separately):
   - Resume cyclosporin;
   - Resume MMF, 1000 mg twice daily;
   - Etritinate 0.25 mg/kg/day in 2 doses and increase to 1 mg/kg/day after 2 weeks;
   - UVB or PUVA radiation;
   - Paquenil, 400 - 800 mg daily;
   - Clofazimine, 300 mg daily;
   - Thalidomide, 100 - 400 mg daily.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. Completion of protocol treatment
2. Excessive toxicity preventing continuation of treatment (including toxic death)
3. Intercurrent death
4. No compliance of the patient (especially refusal to continue treatment)
5. Major protocol violation

11 Required clinical evaluations

Aim of the clinical evaluation during treatment and follow up is to determine response and toxicities. Evaluation of response is described in paragraph 11.4 and appendix A.

11.1 Time of clinical evaluations

- At entry: before start of immunosuppression
- Day 28, 56, 84
- Day 180
- Day 365
- After day 365 every 6 months

11.2 Required investigations at entry, during treatment and during follow up

	At entry	Day 28, 56, 84	Day 180	Day 365	Follow up
Medical history	X	X	X	X	X
Physical examination	X	X	X	X	X
Hematology	X	X	X	X	X
Blood chemistry	X	X	X	X	X
Immunochemistry	X	X	X	X	X
Bone marrow					
Bone marrow aspirate	X		X	X	X[2)]
Bone marrow biopsy	X		X	X	
Specific investigations					
β_2-microglobulin	X				
Creatinin clearance	o.i.	o.i.	o.i.	o.i.	
Skeletal survey	X	o.i.	o.i.	X	X[1)]
X-thorax	X				
ECG	X			X	
Cardiac ejection	o.i.	o.i.	o.i.	o.i.	
Grading of GVHD		X	X	X	X
Additional investigations	o.i.	o.i.	o.i.	o.i.	o.i.
Chimerism		X	X	X	X[1)]

o.i. on indication

1) once a year

2) once a year, twice a year if non-secretory myeloma

11.2.1 Medical history

Standard medical history, with special attention for:

- WHO performance status
- Bone pain
- Infections
- Bleeding tendency

11.2.2 Physical examination

Standard physical examination including body weight and height, with special attention for:

- Macroglossia
- Kyphoscoliosis
- Orthostatic hypotension
- Carpal tunnel syndrome
- Polyneuropathy or other neurologic symptoms
- Edema
- Infections
- Bleeding tendency

11.2.3 Hematology

- Hemoglobin
- Leukocyte count, differential count
- Platelets

Only after allogeneic stem cell infusion:

- Recovery of peripheral blood cells

11.2.4 Blood chemistry

- BUN
- Creatinin
- Liver enzymes
- Total bilirubin
- Alkaline phosphatase
- Total proteins
- Albumin
- LDH

- CRP
- Calcium
- Phosphate
- Sodium
- Potassium
- Uric acid

11.2.5 Immunochemistry

- Quantitative serum M-protein, including immunofixation to confirm CR
- Quantitative urine M-protein in 24 hrs urine, including immunofixation to confirm CR

11.2.6 Bone marrow

- Bone marrow biopsy
- Bone marrow aspirate at entry for:
  - Morphology, immunophenotyping
- Bone marrow aspirate during treatment and follow up for:
  - Morphology

11.2.7 Specific investigations

- Labeling Index (by BRDU) or KI-67 (optional)
- Serum β_2-microglobulin
- Creatinin clearance if increased serum creatinin
- Radiographic skeletal survey including skull, pelvis, vertebral column and long bones
- X-Thorax
- ECG
- Cardiac ejection by scintigraphy or cardiac echo (only on indication)
- Grading of GVHD
- CMV, EBV, HIV, Toxoplasma serology, hepatitis screening

11.2.8 Additional investigations

Only on clinical indication:

- Bleeding time
- Serum viscosity, funduscopy
- Spirometry

11.3 Chimerism evaluation

Chimerism will be evaluated on days 28, 56, 84, 180, 365 and then yearly post-transplant in peripheral blood, according to local protocols.

11.4 Evaluation of response

Response will be evaluated according to EBMT, IBMTR and ABMT criteria (see appendix A) on days 180 and 365 post-transplant, and thereafter at least once a year.

11.5 Donor evaluations

Evaluation of the donor will include the following:

- Complete history and physical examination.
- Lab tests: CBC with reticulocytes and platelet counts, SMAC 12, hepatitis screen, CMV, syphilis, HIV and HTLV I serologies and ABO Rh blood typing. If donor has antibodies against red cell antigens of the recipient, the titers will be determined. Cytotoxic crossmatch between patient and donor (HLA Laboratory).
- No placement of a central line is necessary for G-CSF stimulated PBSC or PBMC collection unless it is determined that the donor has poor venous access. If so a temporary pheresis catheter will be placed at the time of leukapheresis.
- CBC will be checked prior to and after leukapheresis collection, and daily while on G-CSF. Thereafter if clinically indicated.
- The donor will be seen again in the clinic the day after the apheresis is completed.

12 Toxicities

Toxicities will be scored according to the NCI Common Toxicity Criteria, version 2.0 (Appendix B).

12.1 Allogeneic peripheral blood stem cell transplant

Side effects include low blood count, infections, bleeding, and failure of the donor stem cells to grow. Supportive care with red cell and platelet transfusions and antibiotic therapy may be necessary. Graft versus host disease (inflammation of skin, liver and gastrointestinal system), may also occur and require treatment with immune suppressing drugs. In addition, organ damage may occur as a result of radiation or the treatment with immune suppressing drugs. There is a risk that the patient will reject the donor's PBSC and that donor cells will not be detected after transplant. The dose of radiation used is not be expected to cause permanent marrow suppression in the event that graft rejection occurs.

12.1.1 Graft versus Host Disease

The major toxicity associated with allografting or infusion of donor PBSC is GVHD. GVHD has occurred in > 50% of patients.

Diagnosis of GVHD: Skin involvement will be assessed by biopsy with percentage of body surface area involved recorded. GI symptoms suspicious for GVHD will be evaluated by biopsy as indicated. Acute GVHD and chronic GVHD will be graded according to established criteria (appendix E).

12.1.2 Rejection

Rejection is defined as absence of donor T-cell chimerism. Rejection may occur without any increase of donor cells or after engraftment and decline thereafter.

12.2 Total body irradiation

The total body irradiation (TBI) will be delivered with 10 MV photons. The total dose of TBI used in this protocol is 200 cGy (in approximately 15 minutes) to the midline of the body. This dose is much lower than used in conventional transplant protocols, and protection of lungs, kidneys or eyes is not necessary. No severe acute or late side effects from the TBI are expected. Sterility has been associated with TBI, only when higher doses were used. However sterility was induced

already by treatment with High Dose Melphalan as preparative regimen for the autologous stem cell transplantation.

12.3 Mycophenolate mofetil

MMF is a relatively new drug used for suppressing the immune system and it has not been used frequently in bone marrow transplantation. Preliminary studies indicate that this drug is reasonably well tolerated in the transplant setting. There are a small number of patients who have received solid organ transplants and had reversible fall in their red cell or white cell count while receiving MMF. The blood counts will be watched closely and, if significant decrease is noted, dose adjustments or stopping MMF may be indicated. Other uncommon side effects include nausea, vomiting, diarrhea, and abdominal discomfort. Cases of intestinal bleeding have also been reported.

12.4 Cyclosporine A

The immediate effects of this drug may include nausea or vomiting when given orally. Other side effects include the possibility of developing high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. These effects are generally reversible upon decreasing the dose of the drug. An occasional patient has had a seizure but it is unclear whether cyclosporine, other drugs, or a combination of drugs was responsible. Some patients given intravenous cyclosporine for the treatment of GVHD experienced painful sensation in hands or feet or both. The pain subsided with the improvement of the GVHD or when the cyclosporine was switched from the intravenous to the oral form.

Patients may experience a change of liver or kidney function, in which case the dose may be reduced or possibly even stopped for a while. This effect on kidneys seems to increase when other drugs which might cause kidney problems are given at the same time, especially certain antibiotics. Occasionally the kidney damage is severe enough to require the use of an artificial kidney machine (hemodialysis). During treatment cyclosporine blood levels will be monitored to determine if there are increased risks of side effects that warrant changing the dose.

13 Reporting serious adverse events

An Adverse Event (AE) is any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs during or following treatment regardless of the causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the treatment.

Serious Adverse Events (SAE) are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment. Adverse events which are considered as serious are those which result in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- severe/permanent disability
- a congenital anomaly

Note that any death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

Unexpected Serious Adverse Events are those SAE's of which the nature or severity is not consistent with information in the relevant source documents. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as a source document in that country.

Reporting Serious Adverse Events

During protocol treatment all deaths, all SAE's that are life threatening and any *unexpected* SAE must be reported to the HOVON Data Center by fax **within 48 hours of the initial observation of the event**. All details should be documented on the **Serious Adverse Event and Death Report**. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 14 calendar days and sent to the HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

At any time after the completion of protocol treatment, *unexpected* Serious Adverse Events that are considered to be possibly related to protocol treatment and ANY death (regardless the cause) must also be reported to the HOVON Data Center using the same procedure, **within 48 hours after the SAE or death was known to the investigator**.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following :

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The HOVON Data Center will forward all reports within 24 hours of receipt to the study coordinator and the study central datamanager. The report of an SAE will be the signal for the central datamanager to ask the investigator or the responsible local datamanager to complete and send as soon as possible all relevant CRF's for the involved patient with details of treatment and outcome. It is of utmost importance that all SAE's (including all deaths due to any cause) are reported in a timely fashion. Patients without a report of an SAE are implicitly considered alive without SAE. This information will be used in monitoring the incidence of SAE's, the estimation of overall survival and monitoring of safety of experimental treatments.

14 Endpoints

Primary endpoint is:

- progression free survival (PFS)

Secondary endpoints are:

- sustained allogeneic engraftment
- response rate (especially CR)
- overall survival (OS)
- transplant related mortality (TRM)
- incidence of grades 2-4 acute GVHD after transplant
- incidence of chronic extensive GVHD after transplant
- incidence of myelosuppression (ANC < 0.5 $x10^9$/l for > 2 days, platelets < 20 x 10^9/l for > 2 days) after initial PBSC infusion

15 Forms and procedures for collecting data

15.1 CRF's and schedule for completion

LIST OF FORMS

Form nr	Nr of pages	Title
1	2	Registration
2	3	On Study
3	3	Transplant
4	3	Transplant Evaluation
5	2	Post-transplant Laboratory Evaluations
6	3	Response Evaluation
7	2	Acute GVHD
8	2	Chronic GVHD
9	1	Off Treatment
10	2	Follow Up
11	1	Side Effects
12	1	Infection Report
13	1	General Comments
14	1	Prolonged Hypoplasia

Table for filling out forms

	Forms													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Registration	**X**												**(X)**	
On Study		**X**											**(X)**	
Post-transplant			**X**	**X**	**X**	**X**	**(X)**	**(X)**	**X**	**X**	**(X)**	**(X)**	**(X)**	**(X)**
Follow Up						**X**	**(X)**	**(X)**		**X**	**(X)**	**(X)**	**(X)**	**(X)**

(x) fill out if necessary, see instructions

Instructions for completion and sending in of the forms are specified in a separate document together with the forms.

16 Registration

16.1 Registration for NMA Allogeneic SCT

The patient should be registered after evaluation of the first cycle of HDM + Autologous stem cell reinfusion according to the HOVON 50 MM protocol, and before the start of immunosuppression for NMA Allogeneic SCT. Patients need to be registered at the HOVON Data Center of the Erasmus MC - Daniel den Hoed by phone call: +31.10.4391568 or fax +31.10.4391028 Monday through Friday, from 09:00 to 17:00 or via the Internet via TOP (Trial Online Process; http://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.

The following information will be requested at registration:

1. Protocol number
2. Institution name
3. Name of caller/responsible investigator
4. Patient's initials or code
5. Patient's hospital record number
6. Sex
7. Date of birth
8. Patient study number in HOVON 50 MM
9. Date of autologous stem cell reinfusion after 1 cycle of HDM in HOVON 50 MM
10. Planned date of NMA Allo-SCT
11. Eligibility criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number, which will be given immediately by TOP or phone and confirmed by fax or email.

17 Statistical considerations

This is a phase II study with a plan to enroll a total of 40 patients who received VAD and HDM followed by autologous stem cell transplantation in the HOVON 50 MM trial. The study should finish accrual in approximately 3 years with an expected yearly accrual of 15 patients.

17.1 Analysis of efficacy

17.1.1 Progression free survival

In the HOVON 24 MM trial, PFS from myeloablative allogeneic transplantation at 1 year was 66% in patients ≤ 55 years, with 25% TRM. If after 40 patients have been treated estimates of PFS and TRM suggest a benefit of treatment, NMA allo-SCT may be incorporated as standard treatment for patients ≤ 65 years with an HLA-identical sibling. It could also be expanded to high-risk patients who have a MUD donor. This approach would be considered to be potentially efficacious and worthy of study in future trials if observed 1-year PFS is 70% or greater. Moreover, TRM at one year post-transplant should not exceed 15%.

17.2 Analysis of safety

With respect to safety, patients will be monitored for the development of GVHD, myelosuppression and infections. The main risks of this therapy relate to GVHD. There is also a risk of myelosuppression or graft rejection although these should not be fatal. Patients will be closely monitored for unexpected toxicities and, if any serious side effects are observed, the investigators will re-evaluate the appropriate course for the study. At the conclusion of the study, all unexpected toxicities will be summarized and reported. In addition, treatment related mortality will be monitored carefully throughout the study, and stopping rules based on TRM are as follows:

Treatment-related Mortality after PBSC Infusion*:* We would be concerned if the true incidence of transplant-related mortality (TRM, defined as death without evidence of disease progression) exceeded 15% at one year. Therefore, the current study will be terminated if there is ever sufficient evidence suggesting that the true incidence of TRM at 1 year post-transplant exceeds 15%. Sufficient evidence will be taken to be any ratio of transplant-related deaths which causes the lower limit of the two-sided 90% CI of the Kaplan-Meier estimate at 1 year post-transplant to exceed 15%. When the Kaplan-Meier estimate of TRM at 1 year is 100%, the 90% CI is not defined. In that case the 90% CI of TRM just before the last event will be used instead.

This rule will be applied only after a minimum of 3 patients have died from TRM, and at every newly TRM reported subsequently.

The following table summarizes the operating characteristics of this stopping rule:

True probability of TRM	Probability of stopping (1)	Expected number of patients entered (2)
.05	.01	39.8
.10	.06	38.7
.12	.11	37.7
.15	.22	35.8
.18	.37	33.3
.20	.49	31.4
.25	.72	26.6
.30	.89	22.2

(1) represents an estimate of the actuarial probability of stopping due to excess TRM by one year; estimated from 10,000 Monte Carlo simulations
(2) represents an estimate of the expected number of patients that will be entered in this trial. This number is lower than 40 due to the probability that the trial may be discontinued early due to excess TRM; it is an immediate consequence of the 10,000 Monte Carlo simulations performed under (1).
In the actuarial calculation patients will be censored at death not due to TRM or at date last being alive. Patients without SAE report information will be considered still alive without TRM.

17.3 Secondary endpoints

The secondary endpoints are mentioned in paragraph 14. They will be examined separately and reported in a descriptive manner and confidence intervals will be presented for all estimates.

18 Ethics

18.1 Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Edinburgh, Scotland, 2000) and the ICH-GCP Guidelines of 17 January 1997.

18.3 Patient information and consent

Written Informed consent of patients is required before registration. The procedure and the risks and the opinions for post-induction therapy in multiple myeloma will be explained to the patient.

19 Trial insurance

The HOVON insurance program covers all patients from participating centers in the Netherlands according to Dutch law (WMO). The WMO insurance statement can be viewed on the HOVON Web site www.hovon.nl.

Individual participating centers from outside the Netherlands have to inform the HOVON about the national laws regarding the risk insurance of patients participating in a study. If necessary HOVON will extend the insurance to cover these patients.

Intergroup studies.
The HOVON insurance program does not cover the risk insurance of patients from centers participating within another cooperative group taking part in an intergroup study. The other participating groups will cover the insurance of patients registered/randomized through their offices.

20 Publication policy

The final publication of the trial results will be written by the Study Coordinator(s) on the basis of the statistical analysis performed at the HOVON Data Center. A draft manuscript will be submitted to the Data Center and all co-authors (and the sponsor, where applicable) for review. After revision by the Data Center, the other co-authors (and the sponsor), the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the study coordinator(s), the lead investigators of the major groups (in case of intergroup studies), investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion), the statistician(s) and the HOVON datamanager in charge of the trial, and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomized treatment arms may be made publicly available before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study end-points unless the final results of the trial have already been published.

21 Glossary of abbreviations

(in alphabetical order)

AD	Doxorubicin (Adriamycin), Dexamethasone
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ANC	Absolute Neutrophil Count
ATG	Anti-Thymocyte Globulin
BJ	Bence Jones
BM	Bone Marrow
BMT	Bone Marrow Transplant
BRDU	Bromo Deoxy Uridine
BUN	Blood Urea Nitrogen
Ca	Calcium
CAD	Cyclophosphamide, Doxorubicin (Adriamycin), Dexamethasone
CI	Confidence Interval
CKTO	`Commissie voor Klinisch Toegepast Onderzoek' (previously "CKVO")
CML	Chronic Myeloid Leukemia
CMV	Cytomegalovirus
CR	Complete Remission
CRF	Case Report Form
CRP	C-Reactive Protein
CSP	Cyclosporin A
CTC	Common Toxicity Criteria
DCEP	Dexamethasone, Cytosar, Etoposide, Platinum
DLI	Donor Lymphocyte Infusion
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EBMT	European Group for Blood and Marrow Transplantation
EFS	Event Free Survival
EORTC	European Organization for Research and Treatment of Cancer
FISH	Fluorescence In Situ Hybridisation
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastro-intestinal
GVHD	Graft versus Host Disease
GVM	Graft versus Myeloma
HB	Hemoglobin
HDM	High Dose Melphalan
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte histocompatibility Antigen

HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
HSCT	Hematopoietic Stem Cell Transplantation
HSV	Herpes Simplex Virus
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IDM	Intermediate Dose Melphalan
IFM	Intergroup Français de Myelom
IFN	Interferon
IRB	Institutional Review Board
ITT	Intention To Treat
IU	International Units
IV	Intravenous
KCl	Potassium chloride
LDH	Lactate Dehydrogenase
METC	Medical Ethical review committee
MM	Multiple Myeloma
MMF	Mycophenolate Mofetil
NaCl	Sodium Chloride
NCI	National Cancer Institute
NMA	Non Myeloablative
NMSG	Nordic Myeloma Study group
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PBMC	Peripheral Bone Marrow Cells
PBSC	Peripheral Blood Stem Cell(s)
PCP	Pneumocystis Carinii Pneumonia
PD	Progressive Disease
PFS	Progression Free Survival
PO	Per Os
PR	Partial Response
SAE	Serious Adverse Event
SC	Subcutaneous
SCT	Stem Cell Transplantation
SD	Stable Disease
TBI	Total Body Irradiation
TRM	Treatment Related Mortality
ULN	Upper Limit of Normal
VAD	Vincristine, Doxorubicin (Adriamycin), Dexamethasone
VNTR	Variable Number Tandem Repeat
WHO	World Health Organization
WMO	`Wet Medisch-Wetenschappelijk Onderzoek met mensen'

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A. Response Criteria for Multiple Myeloma

Based on EBMT, IBMTR and ABMT criteria (British J. Haemat. 102: 1115-1123, 1998)

Complete response (CR) requires *all* of the following:

1. Absence of the original monoclonal paraprotein (M-Protein) in serum and (10 x concentrated) urine by immunofixation, maintained for at least 6 weeks.
2. < 5% plasma cells in a representative bone marrow aspirate or otherwise in a bone marrow biopsy. Only in patients with non-secretory myeloma, bone marrow investigation must be repeated after an interval of 6 weeks to confirm CR.
3. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude CR)
4. Disappearance of any soft tissue plasmacytoma.

Patients in whom some, but not all, criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Partial response (PR) requires *all* of the following:

1. ≥ 50% reduction of serum M-protein concentration maintained for at least 6 weeks.
2. Reduction in 24 hrs urine M-protein either by ≥ 90% or to < 200 mg, maintained for at least 6 weeks.
3. In patients with non-secretory myeloma, ≥ 50% reduction in plasma cells in a representative bone marrow aspirate, or otherwise bone marrow biopsy, maintained for at least 6 weeks.
4. ≥ 50% reduction in size of soft tissue plasmacytoma.
5. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude PR).

Patients in whom some, but not all, criteria for PR are fulfilled are classified as MR, providing the remaining criteria satisfy the requirements for PR.

Minimal response (MR) requires *all* of the following:

1. ≥ 25% reduction of serum M-protein concentration maintained for at least 6 weeks.
2. ≥ 50% reduction in 24 hrs urine M-protein, maintained for at least 6 weeks.
3. In patients with non-secretory myeloma, ≥ 25% reduction in plasma cells in a representative bone marrow aspirate, or otherwise bone marrow biopsy, maintained for at least 6 weeks.

4. ≥ 25% reduction in size of soft tissue plasmacytoma.
5. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude MR).

No change (NC)

1. Not meeting the criteria of either minimal response or progressive disease.

Progressive disease (for patients without prior response) requires one or more of the following:

1. > 25% increase in serum M-protein level, which must also be an absolute increase of at least 5 g/l and confirmed at least once.
2. > 25% increase in 24 hrs urine M-protein, which must also be an absolute increase of at least 200 mg/24 hrs and confirmed at least once.
3. > 25% increase in plasma cells in a representative bone marrow aspirate or bone marrow biopsy
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new bone lesions or soft tissue plasmacytomas (development of compression fractures does not exclude continued response and may not indicate progression).
6. Development of hypercalcaemia (corrected serum calcium > 2.80 mmol/l) not attributable to any other cause.

Plateau

1. Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.

Relapse from CR requires at least one of the following:

1. Reappearance of serum or urine M-protein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
2. ≥ 5% plasma cells in a representative bone marrow aspirate or bone marrow biopsy
3. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of compression fractures does not exclude continued response and may not indicate relapse).
4. Development of hypercalcaemia (corrected serum calcium > 2.80 mmol/l) not attributable to any other cause.

Progression after PR / MR requires one or more of the following:

1. > 25% increase in serum M-protein level compared to nadir, which must also be an absolute increase of at least 5 g/l and confirmed at least once.
2. > 25% increase in 24 hrs urine M-protein compared to nadir, which must also be an absolute increase of at least 200 mg/24 hrs and confirmed at least once.
3. > 25% increase in plasma cells in a representative bone marrow aspirate or bone marrow biopsy compared to nadir.
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new bone lesions or soft tissue plasmacytomas (development of compression fractures does not exclude continued response and may not indicate progression).
6. Development of hypercalcaemia (corrected serum calcium > 2.80 mmol/l) not attributable to any other cause.

B. Common Toxicity Criteria

The grading of toxicity and adverse events will be done using the NCI Common Toxicity Criteria, CTC version 2.0, revised March 23, 1998. A complete document (19 pages) may be downloaded from the following sites:

http://ctep.info.nih.gov/ctc3/default.htm
http://www.eortc.be (under Documents)
http://www.hovon.nl

A hardcopy may be obtained from the HOVON Data Center on request.

C. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

D. NYHA* scoring list

Grade 1 No breathlessness

Grade 2 Breathlessness on severe exertion

Grade 3 Breathlessness on mild exertion

Grade 4 Breathlessness at rest

The *New York Heart Association functional and therapeutic classification applied to dyspnoea

E. Grading of GVHD

Acute GVHD

Severity of organ involvement

Skin	+1 maculopapular eruption involving less than 25% of the body surface
	+2 maculopapular eruption involving 25-50% of the body surface
	+3 generalized erythroderma
	+4 generalized erythroderma with bullous formation and often with desquamation
Liver	+1 moderate increase in ASAT[1] (150-170 IU) and bilirubin (20-40 μmol/l)
	+2 bilirubin rise 40-75 μmol/l with or without an increase in ASAT
	+3 bilirubin rise 75-200 μmol/l with or without an increase in ASAT
	+4 bilirubin rise to > 200 μmol/l with or without an increase in ASAT
GI	Diarrhea, nausea and vomiting graded +1 to +4 in severity
	The severity of GI involvement is assigned to the most severe involvement noted
Diarrhea	+1 > 500 ml of stool/day
	+2 > 1000 ml of stool/day
	+3 > 1500 ml of stool/day
	+4 > 2000 ml of stool/day

[1]increases in ASAT temporally related to either the onset or worsening of the skin rash

Severity of acute GVHD

Grade I +1 to +2 skin rash
no GI involvement
no more than +1 liver involvement
no decrease in performance

Grade II +1 to +3 skin rash
+1 to +2 GI involvement and/or
+1 to +2 liver involvement
mild decrease in performance

Grade III +2 to +4 skin rash and
+2 to +4 GI involvement with or without +2 to +4 liver involvement
marked decrease in performance with or without fever

Grade IV pattern and severity of GVHD similar to grade III with extreme constitutional symptoms

Chronic GVHD

Limited Localized skin involvement and/or liver function abnormalities

Extensive Generalized skin involvement, or localized skin involvement and/or liver function abnormalities + other organ involvements

F. Patiënteninformatie

Patiënten-informatie behorende bij de studie:
Niet myeloablatieve donor stamceltransplantatie (voor patiënten die deelnemen aan de HOVON 50 studie) in aansluiting op voorbehandeling met hoge dosis chemotherapie met als doel een "Transplantaat versus Myeloom" effect te bewerkstelligen.

Inleiding

Geachte heer, mevrouw,
Uw behandelend arts heeft u voorgesteld aan het hierboven genoemde onderzoek deel te nemen en al het één en ander uitgelegd. Uw toestemming of weigering moet u kunnen baseren op goede voorlichting onzerzijds. Daarom ontvangt u deze schriftelijke informatie, die u rustig kunt (her)lezen en in eigen kring bespreken. Ook daarna kunt u altijd nog vragen voorleggen aan de artsen die aan het einde van deze informatie genoemd staan.

Uw medische situatie en de bestaande mogelijkheden tot behandeling
Bij u is de diagnose multipel myeloom (ziekte van Kahler) gesteld en u neemt deel aan de HOVON 50 studie, waarin de waarde van behandeling met intensieve chemotherapie (=anti-kanker medicijnen) al of niet in combinatie met Thalidomide wordt onderzocht. Dit onderzoek wordt namens HOVON (Stichting Hemato-Oncologie voor Volwassenen Nederland) uitgevoerd in een groot aantal Nederlandse en Belgische Ziekenhuizen.
De mogelijkheid bestaat om na afsluiten van de behandeling volgens de HOVON 50 studie bij u een aanvullende zogenaamde "niet myeloablatieve" donor stamceltransplantatie uit te voeren. Uit bloedonderzoek is namelijk gebleken dat één van uw broer(s) en of zuster(s) geschikt is om voor u als stamcel donor te fungeren. Hieronder zal worden besproken hoe een dergelijke donor stamceltransplantatie wordt uitgevoerd en wat hiervan de eventuele voor- en nadelen zijn.

Wat is een "niet myeloablatieve stamceltransplantatie":
Bij de "standaard" stamceltransplantatie wordt het eigen beenmerg eerst volledig uitgeschakeld door hoge dosis chemotherapie al of niet gecombineerd met lichaamsbestraling. Vervolgens worden (met een infuus) de eigen stamcellen (autologe stamceltransplantatie) of die van een geschikte donor (allogene stamceltransplantatie) toegediend en na uitrijpen gaan deze stamcellen in het beenmerg de nieuwe bloedcellen vormen. In de patiënten informatie van de HOVON 50 hebt u al uitvoerig over de uitvoering van de autologe stamceltransplantatie kunnen lezen.

Bij de “niet myeloablatieve stamcel transplantatie” wordt een veel lichtere voorbehandeling gegeven, die kan bestaan uit een lichte vorm van lichaamsbestraling al of niet gecombineerd met betrekkelijk laag gedoseerde chemotherapie. Door deze minder agressieve behandeling wordt het eigen beenmerg niet volledig uitgeschakeld. Wel zorgt deze behandeling ervoor dat de eigen afweer zodanig wordt verzwakt dat een stamceltransplantaat van een geschikte donor kan “aanslaan”. Door de verzwakte afweer kunnen de donor stamcellen na transplantatie gaan nestelen in het beenmerg en vervolgens uitgroeien. Eerst *samen en naast* de eigen beenmerg stamcellen. Geleidelijk krijgen de donor stamcellen echter de overhand zodat na verloop van tijd - vaak al 1 maand na de transplantatie - in het bloed vrijwel alleen nog maar donor cellen worden aangetroffen.

Donor stamceltransplantatie bij het Multipel Myeloom en het “Transplantaat versus Myeloom” effect

Standaard donor stamceltransplantatie: Voordelen van een donor stamcel transplantatie zijn dat het transplantaat schoon (tumorvrij) is en (vooral) dat er een extra anti-myeloomcel werking van het transplantaat zelf kan uitgaan: het zogenaamde *“Transplantaat versus Myeloom”* effect. Donor afweercellen uit het transplantaat herkennen de tumorcellen als vreemd en ruimen deze op. Hierdoor kan het uiteindelijke effect van een donor stamceltransplantatie beter zijn dan van intensieve therapie met eigen stamcel transplantatie, mede ook omdat als de ziekte na de donor transplantatie weer actief wordt deze vaak goed en zeer langdurig reageert op alleen toediening van bloedcellen van de donor. Hoewel er dus een onomstotelijk “*Transplantaat versus Myeloom*” effect bestaat wordt de ”standaard” donor stamceltransplantatie vrijwel niet meer uitgevoerd bij het multipel myeloom. Dit komt omdat gebleken is dat veel patiënten (20-30%) overlijden aan bijwerkingen van de transplantatie zelf.

Niet myeloablatieve donor stamceltransplantatie: Voordeel van de niet myeloablatieve stamceltransplantatie is dat er veel minder directe bijwerkingen zijn, zodat de behandeling vrijwel poliklinisch kan worden uitgevoerd tot op hogere leeftijd (70 jaar). Hoewel deze behandeling tot nog toe vooral is uitgevoerd bij patiënten die niet in aanmerking kwamen voor de standaard donor transplantatie (vaak vanwege slechte conditie, te hoge leeftijd, geen goede reactie op voorbehandeling), lijkt de kans op overlijden door bijwerkingen van de transplantatie zelf aanmerkelijk lager te liggen (± 10%). Mogelijk ligt dit percentage nog lager bij minder uitvoerig voorbehandelde patiënten met een betere conditie. Bij de ziekte van Kahler zijn vooral goede resultaten bereikt (positief “Transplantaat versus Myeloom” effect) nadat eerst met een autologe (eigen) stamceltransplantatie de ziekte goed was teruggebracht. Omdat de niet myeloablatieve

transplantatie vooral is toegepast bij uitvoerig voorbehandelde (Kahler) patiënten is niet bekend wat de resultaten zijn als ze in een eerdere fase van de ziekte wordt uitgevoerd. Met name of de levensverwachting beter wordt en of de bijwerkingen ervan acceptabel zijn (zie “Doel en achtergrond van het onderzoek”).

Doel en achtergrond van het onderzoek

Het doel van het onderzoek is om:

De effectiviteit van de niet myeloablatieve stamceltransplantatie als aanvulling op intensieve therapie te bepalen.

Te bepalen wat de bijwerkingen van deze behandeling zijn.

Vast te stellen bij welke patiënten niet myeloablatieve donor stamceltransplantatie eventueel *wel* en bij welke patiënten *niet* zinvol is.

Behandelingsplan

Nadat u voldoende hersteld bent van de intensieve behandeling (de Hoge Dosis Melphalan therapie) zult u nogmaals uitgebreid onderzocht worden om vast te stellen hoe u op de voorafgaande behandeling gereageerd hebt en of er geen belemmeringen bij u aanwezig zijn om de transplantatie uit te voeren. Naast routine bloed en urine onderzoek zal uw beenmerg opnieuw onderzocht worden. Ook zal onderzocht worden of u bepaalde virusinfecties hebt doorgemaakt die na de transplantatie eventueel weer actief kunnen worden. Ook zult u op het AIDS virus getest worden. Twee tot zes maanden na de autologe stamceltransplantatie na Hoge Dosis Melphalan zal de niet myeloablatieve stamceltransplantatie worden uitgevoerd.

De transplantatie: De voorbehandeling bestaat uit een eenmalige zogenaamde totale lichaamsbestraling. Deze zal plaatsvinden in zittende houding op een speciaal ontworpen stoel. De stoel wordt halverwege de bestraling gedraaid. Inclusief het draaien is de geschatte duur van de bestraling ca. 15 minuten. Als gevolg van de lage bestralingsdosis zijn geen ernstige bijwerkingen te verwachten. De radiotherapeut zal U hierover nog apart voorlichten op de bestralingsafdeling. Enkele uren na de bestraling krijgt u via een snellopend infuus de stamcellen van uw donor toegediend. Uw donor is 5 dagen met de groeifactor G-CSF behandeld en de stamcellen zijn op de dag van de transplantatie door middel van leucoferese verzameld. Deze procedure hebt uzelf ook ondergaan om stamcellen te verzamelen die gebruikt zijn bij de Hoge Dosis Melphalan therapie. Voor de transplantatie zult u waarschijnlijk 2-3 dagen worden opgenomen. De dag na de transplantatie kunt u in het algemeen weer naar huis.

Deze lage bestralingsdosis heeft op zich geen steriliteit tot gevolg. Echter, steriliteit is wel het gevolg van de voorafgaande behandeling met de “Hoge Dosis Melphalan” bij de autologe stamcel transplantatie.

Onderzoek na afloop van de behandeling

In de periode dat u ontslagen bent na de stamceltransplantatie zult u regelmatig gecontroleerd worden op de polikliniek. Naast routinematige bloed en urine onderzoeken zal ook beoordeeld worden in hoeverre de behandeling succesvol is geweest. Dit laatste houdt in beenmergpunkties 6 en 12 maanden na de stamceltransplantatie en vervolgens een beenmergpunktie 1x per jaar. Ook zal het röntgenonderzoek van het skelet 1x per jaar herhaald worden.

Bijwerkingen van de niet myeloablatieve stamceltransplanatie

De bijwerkingen in de dagen rond de transplantatie bestaan vaak uit misselijkheid en braken. Dit komt door de combinatie van de bestraling en het slikken van medicijnen zoals cyclosporine (neoral) die afstotingsverschijnselen moeten voorkomen. In het algemeen zijn deze klachten goed te bestrijden met anti-misselijkheids tabletten.

De belangrijkste bijwerking van de niet myeloablatieve transplantatie is het optreden van acute en chronische “Graft versus Host Ziekte”. Dit wordt veroorzaakt door afweercellen van de donor, uit het transplantaat, die reageren op de lichaamscellen van de patient. Hierdoor kunnen ontstekingsverschijnselen optreden in de huid (jeukende huiduitslag), de slijmvliezen (droge mond, diarrhee) en in organen zoals de lever (geelzucht). Om deze ongewenste reacties tegen te gaan slikt u vanaf het begin van de transplantatie medicijnen zoals het reeds genoemde cyclosporine en cellcept. Meestal treedt geleidelijk “gewenning” op tussen de transplantaat donorcellen en de eigen lichaamscellen, zodat de afweermedicijnen na een half jaar kunnen worden gestopt. De meeste patiënten krijgen een lichte vorm van acute (in de eerste 3 maanden na de transplantatie) of chronische Graft versus Host ziekte die bijvoorbeeld met huidzalven goed te controleren is. Soms is de ontstekingsreactie echter zodanig heftig dat extra medicijnen zoals prednison moeten worden voorgeschreven. Soms blijft de Graft versus Host ziekte langdurig (maanden tot mogelijk zelfs jaren) bestaan, zich onder andere uitend in slikklachten (droge mond, verdikte pijnlijke slijmvliezen), chronisch ontstoken huid en pijnlijke gewrichten. Hierdoor moeten de afweermedicijnen ook langdurig ingenomen worden, waardoor ook de verhoogde gevoeligheid voor infecties blijft bestaan. De chronische Graft versus Host ziekte is waarschijnlijk de belangrijkste bijwerking van niet myeloablatieve stamceltransplantatie die in zijn meest ernstige vorm kan leiden tot langdurige ernstige lichamelijke en mogelijk ook psychische problemen. De verwachting is dat chronische Graft versus Host ziekte bij 10 tot 20% van de patiënten zal

optreden, waaronder mogelijk ook een aantal patiënten met de “ernstige” vorm van deze aandoening.
Door de verminderde afweer bestaat er een verhoogde gevoeligheid voor infecties vooral in de eerste 3 maanden na de transplantatie. Met name kunnen virusinfecties (zoals het CMV virus) die u mogelijk al hebt doorgemaakt, na de transplantatie weer actief worden. Om deze reden wordt u kort na de transplantatie veelvuldig gecontroleerd (1 tot 2 x per week). Door middel van bloedonderzoek kan een aantal infecties in een vroeg stadium (nog voordat er symptomen zijn) worden aangetoond en soms zal uit voorzorg al behandeling (in het ziekenhuis of op de polikliniek) plaats vinden.

Deelname

Deelname aan de studie is geheel vrijwillig. Er zal u gevraagd worden of het u geheel duidelijk is wat de studie inhoudt, zodat u een verantwoorde beslissing kunt nemen. U bent geheel vrij uw medewerking aan het onderzoek te weigeren. U zult dan verder behandeld worden volgens het oorspronkelijke HOVON 50 schema. Dit zal geen consequenties hebben voor de relatie met uw arts. Mocht u verdere vragen hebben kunt u altijd contact opnemen met ondergetekenden of met de andere artsen van de afdeling Hematologie. Uw huisarts zal, als u daar geen bezwaar tegen hebt, van uw eventuele deelname aan de studie op de hoogte worden gebracht. Dit is van groot belang voor adequate begeleiding van zijn of haar kant.

Voor- en nadelen

Als u aan de studie mee doet, reageert u mogelijk beter op de behandeling en duurt het mogelijk langer voordat de ziekte terug komt. Of met deze behandeling definitieve genezing mogelijk is, is niet bekend. Het is zeker niet uitgesloten dat er extra bijwerkingen optreden o.a. ten gevolge van afstotingsverschijnselen zoals huiduitslag, droge slijmvliezen of misselijkheid ten gevolge van de medicijnen die u moet slikken. Ook is het mogelijk dat u moet worden opgenomen om eventuele infecties te behandelen. Tenslotte, ook als u zelf geen profijt van de behandeling heeft kan de informatie van deze studie van belang zijn voor de behandeling van andere patiënten met een kwaadaardige aandoening.

Vertrouwelijkheid (Privacy)

Onderzoeksgegevens kunnen slechts door daartoe geautoriseerde medewerkers van overheidsinstanties, medewerkers van het ziekenhuis en bevoegde instanties buiten de kliniek (zoals de medewerkers van de HOVON die verantwoordelijk zijn voor het verzamelen van de gegevens) worden ingezien. Onderzoeksgegevens zullen worden gehanteerd met inachtneming van de wet persoonsregistratie en het privacyreglement van het ziekenhuis. Alle medische

gegevens die tijdens deze studie worden verzameld zullen worden voorzien van een codenummer. Ook bij eventuele publicaties zullen uw persoonsgegevens niet achterhaald kunnen worden. De persoonsgegevens zullen niet gebruikt worden op studiedocumentatie.

Schade

De opdrachtgever van dit onderzoek, de Stichting HOVON (Hemato-Oncologie voor Volwassenen Nederland), heeft u verzekerd in verband met eventuele schade die u zou kunnen lijden als gevolg van uw deelname aan dit onderzoek. Het betreft de schade door overlijden of letsel die zich openbaart gedurende de deelname aan dit onderzoek en deze verzekering is een zogenaamde risico-verzekering, wat inhoudt dat de verzekering ongeacht of het onderzoek verwijtbaar onzorgvuldig is geweest, de schade door overlijden of letsel uit zal keren tot maximaal de daarvoor gestelde bedragen.
Het bedrag waarvoor de verzekering is gesloten is maximaal € 453.781,00 voor de schade per proefpersoon, met een maximum van € 6.806.704,00 voor de schade van alle proefpersonen tezamen die deelnemen aan het onderzoek, en € 9.075.605,00 voor de totale schade die zich per verzekeringsjaar bij proefpersonen heeft geopenbaard bij alle onderzoeken die opdrachtgever per verzekeringsjaar laat uitvoeren.
Indien bovengenoemde bedragen de schade niet volledig dekken en aangetoond kan worden dat de uitvoering van het onderzoek onzorgvuldig is geweest dan kunt u hiernaast ook het ziekenhuis dat opdracht gegeven heeft tot het onderzoek of het ziekenhuis waar het onderzoek is uitgevoerd aansprakelijk stellen.

De verzekering dekt niet de:
schade waarvan op grond van de aard van het onderzoek (nagenoeg) zeker was dat deze zich bij de proefpersoon zou voordoen;
schade die zich bij nakomelingen openbaart als gevolg van een nadelige inwerking van het onderzoek op het genetisch materiaal van de proefpersoon;
schade door aantasting van de gezondheid van de proefpersoon die zich ook zou hebben geopenbaard wanneer de proefpersoon niet aan dit onderzoek had deelgenomen;
schade, die het gevolg is van het niet volledig opvolgen door de proefpersoon van aanwijzingen zoals deze in de patiënteninformatiebrief beschreven staan.

De verzekering is afgesloten bij Zurich Schade te Den Haag onder de voorwaarden voor de verzekering van proefpersonen no. 01121999, onder polisnummer 624.469.703.

Weigeren voor en tijdens het onderzoek

Uw arts heeft u verteld over het doel van dit onderzoek en u gevraagd om er aan mee te werken. U bent uiteraard vrij om uw medewerking aan dit onderzoek te weigeren. Als u besluit niet mee te doen, zult u verder behandeld worden volgens het oorspronkelijke HOVON 50 schema. Ook indien u nu toestemming geeft, kunt u die later zonder opgave van redenen weer intrekken. Wat u ook besluit, het zal geen consequenties hebben voor de verzorging en begeleiding van uzelf en uw familie. De behandeling zal zo nauwkeurig mogelijk volgens vooropgesteld plan verlopen. Het kan natuurlijk gebeuren dat uw lichamelijke reacties of nieuw ontdekte feiten ons tot veranderingen dwingen. Die zullen direct met u besproken worden, zodat u de gelegenheid krijgt te overwegen al of niet met het onderzoek door te gaan. Wel vragen wij van u de voorschriften van uw behandelend arts goed op te volgen en u niet, zonder diens medeweten, elders te laten behandelen.

Tenslotte, u bent verzocht deel te nemen aan medisch wetenschappelijk onderzoek. Dat onderzoek wordt uitgevoerd nadat goedkeuring is verkregen van de Raad van Bestuur/directie van het ziekenhuis na advies van de Medisch Ethische Commissie. De voor dit onderzoek internationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen.

Hoe te handelen bij klachten

Als u klachten heeft over het onderzoek, kunt u dit melden aan de onderzoeker. Wilt u dit liever niet, dan kunt u contact opnemen met het Bureau Patiëntenservice. Patiëntenservice locatie AZU is te vinden in de centrale hal naast de centrale opnamebalie. Telefoon (030) 2504468.

Nadere informatie

Mocht u verdere vragen hebben, dan kunt u die voorleggen aan uw behandelend specialist of aan:

.....[naam/namen betrokken specialisten]

.....

.....

Als onafhankelijk arts kunt u raadplegen:

Dr. K. Nieuwenhuis

Afdeling Hematologie / UMCU

030-2507655

Deze arts is niet bij het onderzoek betrokken.

TOESTEMMINGSVERKLARING
voor deelname aan het wetenschappelijk onderzoek:

Niet myeloablatieve donor stamceltransplantatie (voor patiënten die deelnemen aan de HOVON 50 studie) in aansluiting op voorbehandeling met hoge dosis chemotherapie met als doel een "Transplantaat versus Myeloom" effect te bewerkstelligen.

Ik ben naar tevredenheid over het onderzoek geïnformeerd. Ik heb de schriftelijke informatie goed gelezen. Ik ben in de gelegenheid gesteld om vragen te stellen over het onderzoek. Mijn vragen zijn naar tevredenheid beantwoord. Ik heb goed over deelname aan het onderzoek kunnen nadenken. Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden behoef te geven.
Ik stem vrijwillig toe met deelname aan het onderzoek.

Naam : .....

Adres : .....

Woonplaats : .....

Geboortedatum : .....

Handtekening : ..... Datum: .....

Ondergetekende verklaart, dat de hierboven genoemde persoon zowel schriftelijk als mondeling over het bovenvermelde onderzoek geïnformeerd is. Hij/zij verklaart tevens, dat een voortijdige beëindiging van de deelname door bovengenoemde persoon, van geen enkele invloed zal zijn op de zorg die hem of haar toekomt.

Naam : .....

Functie : .....

Handtekening : ..... Datum: .....

Dit formulier is bestemd voor onderzoek met meerderjarigen, die wilsbekwaam zijn. Bij dit soort onderzoek moet door de betrokkenen zelf toestemming worden verleend.