A randomized phase III study on the effect of Thalidomide combined with Adriamycin, Dexamethasone (AD) and High Dose Melphalan in patients with multiple myeloma

PROTOCOL

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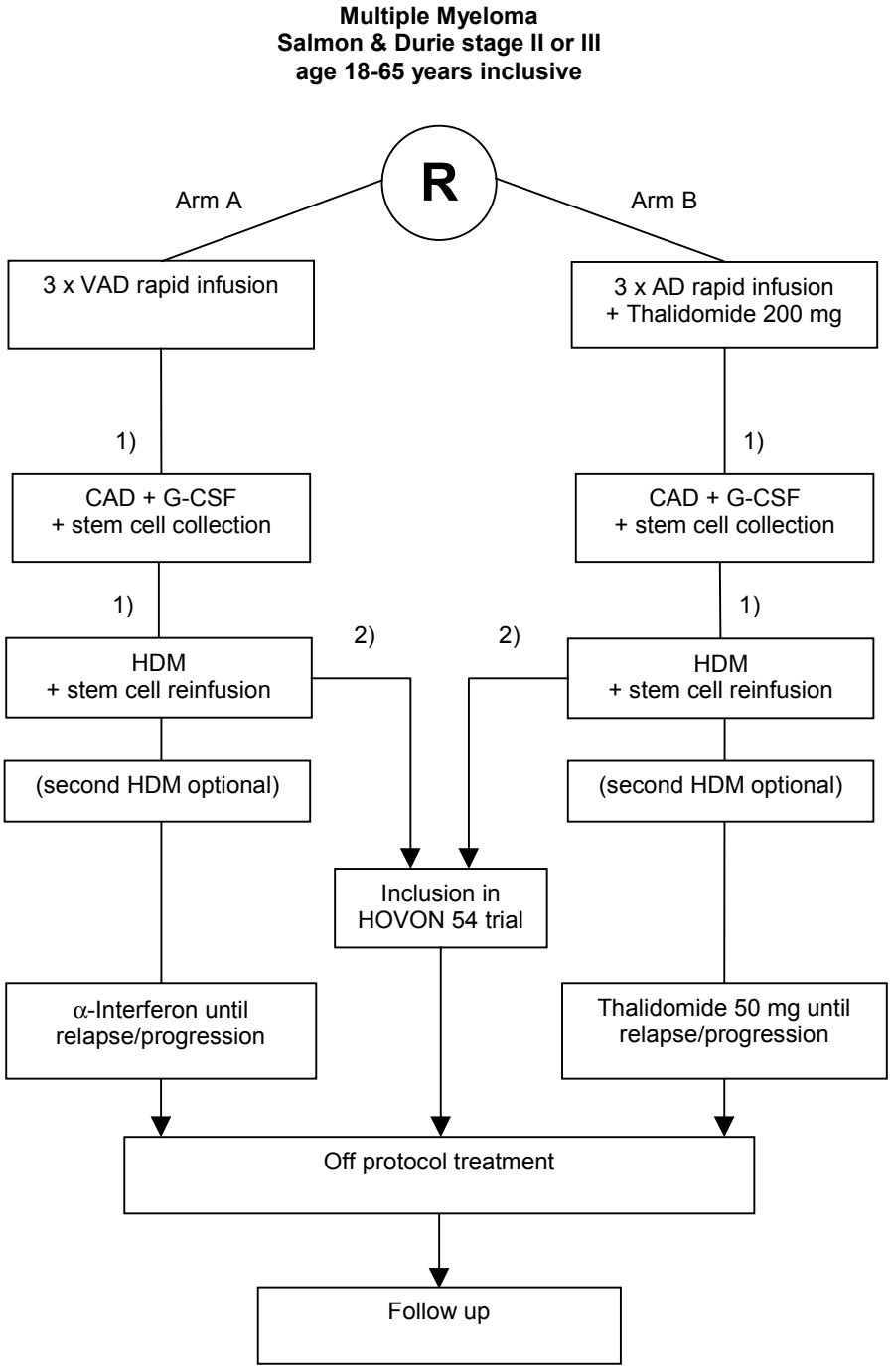
1 Scheme of study



1) Patients who do not meet the inclusion criteria for CAD or HDM but with a CR, PR or MR, may proceed with 3 more cycles of VAD (arm A) or AD with Thalidomide (arm B), followed by IFN maintenance (arm A) or Thalidomide maintenance (arm B) until progression

2) Patients with an HLA-identical family donor who meet the eligibility criteria may be included in the HOVON 54 trial to proceed with non myeloablative allogeneic stem cell transplantation after the first course of HDM

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3 Synopsis

Study phase	Phase III
Study objectives	Evaluation of the effect of Thalidomide in addition to AD and High Dose Melphalan
Patient population	Patients with multiple myeloma, previously untreated, Salmon & Durie stage II or III, age 18-65 years inclusive
Study design	Prospective, multicenter, randomized
Duration of treatment	Expected duration of induction, stem cell collection and intensification (with or without Thalidomide) is 5 - 7 months. Thalidomide will be continued as maintenance until relapse or progression; however it will be discontinued early when the patient has not at least a PR 3 months after Melphalan. In patients not randomized to Thalidomide, maintenance therapy with α-Interferon will be given until relapse or progression
Number of patients	450 patients registered and randomized
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: III 2001 End of recruitment: III 2005

4 Investigators and study administrative structure

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4.1 Cytogenetic review

Each cytogeneticist, responsible for the cytogenetic analysis of the multiple myeloma patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study. A filled out cytogenetic form together with 2 representative karyotypes and a copy of the original cytogenetic report is requested to be sent within 3 months to the HOVON Data Center for central review.

5 Introduction

5.1 Conventional therapy

Multiple myeloma is a hematological malignancy characterized by a proliferation of monoclonal plasma cells, which produce a homogeneous immunoglobulin (M-protein) which can be detected in the serum and/or the urine. It accounts for approximately 1% of all malignancies and 10% of hematological cancers.[1] For several decades intermittent Melphalan and prednisone has been the treatment of choice. Many trials with combination chemotherapy have been performed, but these did not result in an improved outcome as compared to Melphalan and prednisone.[2,3] Fifty to sixty percent of patients respond to conventional chemotherapy and only a minority (< 5%) of patients achieve a complete response.[4] Virtually all patients succumb to refractory disease and the median overall survival is less than 3 years. Even after having achieved a response, patients may remain symptomatic due to a considerable residual tumorload.

5.2 Intensive treatment

High dose chemotherapy for myeloma was introduced in 1983 showing for the first time that in a substantial percentage of patients complete remissions could be induced.[5] Morbidity and mortality however was high, but was strongly reduced later by the application of autologous stem cell rescue. Bone marrow was the source of stem cells in the first studies, peripheral blood stem cells (PBSC) are now routinely applied as autologous rescue.[6]

So far one randomized study has been published which showed that autologous transplantation was superior to conventional treatment regarding response rate, event-free and overall survival. In this study patients under 65 years were randomized at diagnosis to receive VBAP/VMCP or High Dose Melphalan 140 mg/m^2 and TBI 8 Gy supported with autologous bone marrow collected after 2 courses of VBAP/VMCP.[7] In 1994 the Nordic Myeloma Study Group (NMSG) started a study with high-dose chemotherapy in newly diagnosed patients under 60 years.[8] After induction therapy with VAD followed by stem cell collection after Cyclophosphamide 4 g/m^2 and G-CSF, patients received

Melphalan 200 mg/m^2 with stem cell rescue. Survival in the intensive group was significantly prolonged as compared to the control group. The control patients were selected from a historic population of 313 patients identified from 5 previous population-based Nordic studies. Of these, 274 fulfilled the eligibility criteria for the high dose therapy in the NMSG group.

5.3 Double transplantation

Attempts have been made to improve the outcome of myeloma by performing double transplants. The rationale of this approach was based on the observation that the achievement of CR after intensive therapy was a favourable prognostic factor for EFS and OS. The largest series of double transplants has been performed by the group led by Barlogie.[9] In previously untreated patients the CR rate increased from 26% after the first transplant to 41% after the second. Median OS and EFS durations were 68 months and 43 months, respectively. On multivariate analysis, superior EFS and OS were observed in the absence of unfavourable karyotypes (11q breakpoint abnormalities, -13, or 13-q) and with a low β_2-microglobulin at diagnosis. Using case-matched registry data as controls double transplants improved response rate, EFS and OS as compared to conventional treatment. In a recent update of results of tandem transplants in 1000 patients the adverse impact of chromosome 13 deletion was established.

In a recently completed randomized study by the “Intergroup Français de Myelom” (IFM), single versus double stem cell transplantation was compared in previously untreated patients. The results show that patients with a low β_2-microglobulin at diagnosis had a slightly better OS after double transplants.[10] However no improvement of outcome was found in patients with unfavourable prognostic factors like a high β_2-microglobulin and/or deletion of chromosome 13.[11] A retrospective EBMT registry study showed that double transplants, planned or unplanned at the time of the first transplant may be superior to single transplants. Cavo et al found in a small series of patients significantly improved CR rate and EFS in patients following double transplant.[12]

In 1996 HOVON initiated a phase III study in which single intensive therapy without stem cell rescue was compared with double high-dose chemoradiotherapy including stem cell rescue. After induction therapy with VAD patients were randomized between arm A: High Dose Melphalan divided into 2 courses of i.v. Intermediate Dose Melphalan (IDM, Melphalan 70 mg/m^2) followed by maintenance therapy with α-Interferon and arm B: High Dose Melphalan divided into 2 courses of IDM followed by myelo-ablative treatment (Cyclophosphamide,120 mg/m^2 and TBI 8 Gy) with PBSCT followed by maintenance with α-Interferon. Stem cells were mobilized after VAD with Cyclophosphamide 4 g/m^2 and G-CSF. The study was closed April 1, 2000, after the inclusion of 453 patients. An interim analysis performed in January 2001 showed that there is an ongoing improvement of the response rate with every treatment step. However overall survival and event

free survival were not different between the two treatment arms. For definite firm conclusions about the effectiveness of tandem transplants further follow-up of the French randomized study seems warranted.

5.4 Thalidomide

Thalidomide prescribed in the early sixties as sleep inducing drug was withdrawn after the appearance of reports of teratogenecity and phocomelia. Because of its broad spectrum of pharmacological and immunological effects it has returned in modern medicine today and is now used in a wide spectrum of diseases like erythema nodosum leprosum and refractory Becet's disease.[13,14]

Recently it was discovered that Thalidomide has substantial antitumor activity in patients with advanced myeloma.[15] Eighty-four previously treated patients, including 76 with a relapse after high dose chemotherapy, received oral Thalidomide as a single agent for a median of 80 days. The starting dose was 200 mg/day and dose escalation with 200 mg was performed every 2 weeks until a maximum of 800 mg/day. Total response was 32%. In 80% of responding patients M-protein levels began to drop within two months from start of therapy. Responses also included reduced bone marrow plasma cell infiltration and improved general status. After 12 months of follow-up EFS and OS for all patients was 22% and 58% respectively. At least 30% of patients had mild to moderate side effects - constipation, somnolence, neuropathy, rash, weakness and fatigue- while 10% of patients had severe adverse effects. Side effects were most frequent in the group with the higher Thalidomide dosis. The promising results of Thalidomide in refractory myeloma have been confirmed by several other groups. Juliussen et al observed frequent (43%) good partial remissions from Thalidomide including best response ever in 23 patients with advanced and refractory myeloma.[16] In other studies comparable response rates were achieved.[17-20]

The mechanisms of action of Thalidomide are still not clear. Bone marrow vascularization is strongly increased in myeloma and it may be that Thalidomide inhibits angiogenesis thereby inducing apoptosis of myeloma plasma cells.[17,21,22] The microvascular density of bone marrow however did not change in responding patients. Other possible mechanisms of action may include a direct apoptosis inducing effect on myeloma cells, or indirectly influencing the growth and survival of myeloma cells by modulating adhesion molecules or the secretion of cytokines.

The optimal dose of Thalidomide is not known. The maximum tolerated dose varies substantially among patients. However very few patients tolerate the higher doses of 600 - 800 mg. The observation that in most responding patients M-protein levels begin to drop within the first weeks of treatment suggests that dose escalation may not be necessary to induce responses in myeloma and in that way unnecessary side effects can be avoided. The efficacy of low dose Thalidomide

has already been confirmed in clinical studies.[23] A recent analysis in 138 patients indicates that the duration of disease remissions increases with the achieved cumulative dose of Thalidomide (B. Barlogie, personal communication).
Recently the outcome of several studies with Thalidomide alone or combined with Dexamethasone or Doxorubicin were presented at the VIIIth Myeloma Workshop (May 2001, Banff, Alberta, Canada). Important is that Thalidomide, especially when it is combined with Dexamethasone and Doxorubicin, may increase the risk on Deep Venous Thrombosis (DVT). The mechanism sofar is unknown. Since then two reports were published describing the increased incidence of DVT when combined with VAD. Osman et al described symptomatic DVT in 4 of the 15 patients (27%) receiving VAD in previously untreated patients.[36] Zangari and Barlogie et al described that in patients included in the Total Therapy II study, DVT developed in 14 of 50 patients (28%) who were randomly assigned to receive Thalidomide but in only 2 of 50 patients (4%) not given the agent.[37] All DVT's occurred during the first 3 months of induction therapy when the patients received multi-agent treatment including Doxorubicin and Dexamethasone. Thalidomide was resumed in 75% of patients receiving anticoagulation therapy. In the Total Therapy II study anticoagulation prophylaxis with low dose coumarines is now given to all patients randomized to Thalidomide in combination with multi-agent therapy during the first 3 months of induction therapy.

5.5 Maintenance therapy with α-Interferon

A meta-analysis of 30 randomized trials in multiple myeloma including more than 3000 patients, with α-Interferon either as combined IFN-chemotherapy or as maintenance, was recently published.[24] Interferon maintenance therapy as compared to no maintenance, lead to a 4.4 months ($P<0.01$) and 7 months ($P<0.01$) prolongation of relapse-free and overall survival, respectively. In this meta-analysis no differentiation was made between IFN given after high dose or after conventional treatment. The Royal Marsden Group evaluated α-Interferon given as maintenance in patients with a response to High Dose Melphalan in a randomized fashion.[25] At a median follow up of 52 months the progression-free survival from HDM was 46 months in the α-Interferon arm versus 27 months in the control group ($P<0.025$), and overall survival was also significantly better for the α-Interferon arm ($P=0.006$). At a median follow up of 77 months, most of the patients had succumbed to their disease and the survival advantage which was noted at the 4½ year follow up had ceased to exist. The European Bone Marrow Transplantation group found in a multivariate analysis that patients who received IFN had a significant prolonged survival.[26]

5.6 Prognostic factors

Recently, similar to what has been found in acute leukemia, data have been published indicating that specific chromosomal abnormalities have prognostic significance in multiple myeloma. Using conventional cytogenetics, Tricot et al found that partial or complete deletion of chromosome 13 and abnormalities of chromosome 11, present in 10-15% of untreated myeloma, were strong adverse prognostic factors in patients treated with tandem transplantation.[27] Using interphase FISH with specific probes for the retinoblastoma gene (rb-1) the frequency of chromosome 13 deletions was much higher than found with metaphase analysis and varied between 33% and 42% in different studies.[13,28-30] Despite the fact that this technique revealed 13q14 deletions in a much higher frequency as did metaphase analysis, the presence of abnormal chromosome 13 remained the single most significant adverse prognostic factor in patients treated with conventional-dose or high-dose chemotherapy.[31,32] It is obvious that in every prospective myeloma trial “classic” metaphase analysis and interphase FISH to detect abnormal chromosomes 11 and 13 should be part of the pretreatment staging of patients.

5.7 Rationale of the study

This is a phase III study to test the efficacy and feasibility of Thalidomide combined with intensive treatment as compared to intensive treatment only in younger patients with multiple myeloma in relation to established MM prognostic factors. The rationale for combining Thalidomide with chemotherapy is based on the different mechanisms of actions and the potential synergism of Thalidomide and cytostatics and/or Dexamethasone. These assumptions were confirmed in an animal breast cancer model which showed that “angiotherapy” with Thalidomide combined with doxorubicin and cyclophosphamide had greater antitumor activity than chemotherapy alone.[33] The feasibility and efficacy of Thalidomide combined with chemotherapy was also found in human myeloma as demonstrated by the induction of CR in patients with plasma cell leukemia and relapsed refractory disease by the combination of Thalidomide with the DCEP regimen.[34] The rationale for “low dose“ Thalidomide is based on the observation that refractory myeloma patients may be sensitive to low doses given over a prolonged period of time and the lack of evidence for a dose-response relation. In addition, the higher doses of Thalidomide are associated with severe side effects, which makes high dose Thalidomide unacceptable for induction and maintenance therapy. Novel data on the strong prognostic impact of chromosomal aberrations in patients with multiple myeloma make it possible to divide these patients into different prognostic groups. Therefore the potential benefit of Thalidomide can be evaluated in standard-risk patients (serum β_2-microglobulin $\leq$ 3 μg/l and normal chromosome 13 as determined by FISH) and high-risk patients (β_2-microglobulin > 3 μg/l and/or abnormal chromosome 13 as determined by FISH).

The protocol allows to apply two courses of intensified treatment with stem cell rescue, either immediately or with the second course given at relapse or progression. As has been described above, the final analysis of different studies (IFM 94, HOVON 24 MM) has to be awaited for definite conclusions about the impact of double intensification.

6 Study objectives

- To assess the efficacy of Thalidomide combined with intensive chemotherapy in comparison with intensive therapy alone in patients with previously untreated multiple myeloma, as measured by the event free survival. Events are induction failure, disease progression and death from any cause.
- To evaluate the response rate, complete response rate, overall survival and progression free survival.
- To assess the safety and toxicity of Thalidomide combined with intensive chemotherapy.
- To assess the value of risk factors at diagnosis, including β_2-microglobulin and abnormalities of chromosomes 11 and 13 as analyzed in bone marrow plasma cells by karyotyping and FISH, for individual patients with myeloma who are treated with Thalidomide.

7 Study design

Details of all treatments (dose and schedule) are given in 9.1-9.7.

Patients with multiple myeloma, meeting all eligibility criteria (see 8.1) will be randomized on entry between:

Arm A: intensive chemotherapy alone followed by maintenance therapy with α-Interferon (Roferon®)
or
Arm B: intensive chemotherapy with Thalidomide followed by maintenance with Thalidomide

Patients may proceed to non myeloablative AlloSCT, therefore HLA typing of the patient and family should be performed within three months after inclusion in this trial.

7.1 Induction chemotherapy with Vincristine, Adriamycin and Dexamethasone (VAD) or with Adriamycin and Dexamethasone (AD)

All patients will be given 3 cycles of induction chemotherapy. Dosages of (Vincristine), Adriamycin and Dexamethasone are according to the original VAD scheme (Vincristine, Adriamycin, Dexamethasone), with the exception that the dosage of Dexamethasone is the same in all three cycles. Vincristine is omitted in the Thalidomide arm because of the high risk of polyneuropathy when it is combined with Thalidomide.
Patients will be evaluated for response after cycle 3.
Patients who meet the inclusion criteria for CAD and stem cell collection (see 9.3.1), will continue with CAD. Patients who do not meet these inclusion criteria but who are in CR, PR or MR are strongly recommended to be treated as described in paragraph 7.6. Otherwise they go off protocol treatment.

7.2 Stem cell mobilization and collection

In all eligible patients (see 9.3.1) stem cell collection will be performed after CAD (Cyclophosphamide, Adriamycin, Dexamethasone) chemotherapy and G-CSF (Neupogen® SingleJect®).
Patients will be evaluated for response after stem cell collection.

7.3 High Dose Melphalan

All patients who meet the inclusion criteria for intensification (see 9.4.1) will be treated with High Dose Melphalan 200 mg/m² followed by autologous stem cell reinfusion. In patients with renal insufficiency (creatinin ≤ 40 ml/min) the Melphalan dose should be reduced to 100 mg/m².
Patients in a hospital with a policy of double intensification will receive the second course of High Dose Melphalan between 2 and 3 months after the first course.
Patients will be evaluated for response after each course of High Dose Melphalan.

7.4 Thalidomide

Patients randomized to arm B (with Thalidomide) will be given Thalidomide 200 mg daily from day 1 throughout the 3 AD cycles. Thalidomide dose may be escalated to maximally 400 mg in case of good tolerability. Thalidomide is stopped 2 weeks before CAD.

Thalidomide maintenance, 50 mg daily, will start immediately after the first course of HDM. Thalidomide is then continued until progression. Thalidomide is also stopped when a patient has not achieved at least a PR 3 months after the last course of High Dose Melphalan.

7.5 Maintenance therapy with α-Interferon

In patients randomized to arm A (standard arm) who meet the inclusion criteria for α-Interferon (Roferon®) maintenance (see 9.5.1), maintenance will start between 2 and 3 months after the last course of High Dose Melphalan.
α-Interferon is continued until progression. It is also stopped when a patient has not achieved at least a PR 3 months after start of IFN maintenance.

7.6 Treatment of patients in CR, PR or MR who do not meet the inclusion criteria for stem cell mobilization or intensification

For patients who do not meet the inclusion criteria for either stem cell mobilization (see 9.3.1) or intensification (see 9.4.1) but who achieved a CR, PR or MR, it is strongly recommended to continue the treatment with 3 more cycles of (V)AD (see 9.2) with or without Thalidomide according to their randomization arm, followed by maintenance with IFN (arm A) or Thalidomide (arm B) until progression. Maintenance therapy with IFN or Thalidomide will also be stopped when a patient has not achieved at least a PR 3 months after start of maintenance.

7.7 Non-myeloablative allogeneic transplantation (HOVON 54)

Patients with an HLA-identical family donor may be included in the HOVON 54 trial “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.”
Eligibility criteria can be found in the HOVON 54 protocol. Since inclusion in the HOVON 50 trial is an eligibility criterium for the HOVON 54 trial, all patients who are planned for inclusion in the HOVON 54 trial must be entered into the HOVON 50 trial first.
Patients will be treated according to their allocated treatment arm until 1 HDM course has been completed and evaluated. Eligible patients may then be included in the HOVON 54 trial. A patient will go off protocol treatment at the time of transplant in the HOVON 54 trial (see 9.7 for details).

8 Study population

8.1 Eligibility for registration

All eligible patients have to be registered and randomized before start of treatment (see 16.1).

8.1.1 Inclusion criteria

- Patients with a confirmed diagnosis of multiple myeloma stage II or III according to the Salmon & Durie criteria (see appendix A);
- Age 18-65 years inclusive;
- WHO performance status 0-3 (see appendix D);
- Negative pregnancy test at inclusion if applicable;
- Written informed consent.

8.1.2 Exclusion criteria

- Known intolerance of Thalidomide;
- Systemic AL amyloidosis;
- Previous chemotherapy or radiotherapy except 2 cycles of Melphalan/Prednisone or local radiotherapy in case of local myeloma progression;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E) ;
- Significant hepatic dysfunction (serum bilirubin $\geq$ 30 μmol/l or transaminases $\geq$ 2.5 times normal level), unless related to myeloma;
- Patients known to be HIV-positive;
- Patients with active, uncontrolled infections;
- 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;
- Patients who are not willing or capable to use adequate contraception during the therapy (all men, all pre-menopausal women);
- Patients $\leq$ 55 years with an HLA-identical sibling who will undergo **myeloablative** AlloSCT.

9 Treatments

All men and pre-menopausal women should use adequate contraception during the study. Sperm should be frozen from men with child wish before start of treatment.

9.1 Thalidomide

Thalidomide will be administered only to patients randomized to arm B.

Agent	Dose/day	Route	Days
Thalidomide	200 mg Dose escalation to maximally 400 mg optional	p.o.	Start day 1 of first AD Stop 2 weeks before start CAD
Thalidomide	50 mg	p.o.	Start immediately after the first course of HDM. Stop after progression, or when not at least in PR 3 months after last course HDM

The starting dose will be 200 mg/day. The daily Thalidomide dose may be escalated to maximally 400 mg in case of good tolerability (optional). Thalidomide will be administered daily from day 1 throughout the 3 AD cycles. It will then be stopped 2 weeks before the start of CAD to facilitate optimal stem cell collection. Thalidomide will not be resumed between stem cell collection and the first course of HDM.
Thalidomide maintenance 50 mg/day will start immediately after the first course of HDM.
Thalidomide will be stopped after progression and also in patients who have not achieved at least a PR 3 months after the last course of HDM.
When Thalidomide maintenance after HDM is interrupted for more than 6 weeks, it is regarded as end of Thalidomide maintenance and the patient will go off protocol treatment.

Assessment of response during Thalidomide maintenance is described in paragraph 11 and appendix B.

9.1.1 Special management orders in conjunction with Thalidomide

- Due to increased risk on Deep Venous Thrombosis (DVT) during treatment with Thalidomide, especially when it is combined with anthracyclines and dexamethasone, patients should receive thrombosis prophylaxis with low molecular heparine during induction therapy with AD + Thalidomide:
  Fraxiparine 2850 IE anti-Xa = 0.3 ml, sc. (> 90 kg: 5700 IE anti-Xa = 0.6 ml) 1 dd.
  Start day 1 of first AD until 1 week before start of CAD. Thrombosis prophylaxis should also be given when a patient is treated with additional AD + Thalidomide cycles (see 7.6).
- In patients who do not tolerate Thalidomide 200 mg the dose may be adjusted to 100 or 50 mg/day eventually after interruption.

9.1.2 Treatment of Deep Venous Thrombosis

When a DVT occurs during Thalidomide treatment, Thalidomide should be interrupted until the DVT has been resolved. Treatment of DVT is according to local protocol. As soon as the DVT has been resolved, Thalidomide can be resumed according to protocol.
DVT during induction therapy is no contra-indication for low dose Thalidomide maintenance therapy (9.6). Also, it is no indication for thrombosis prophylaxis during Thalidomide maintenance unless additional DVT risk factors like FV Leiden are present.

9.2 Induction therapy

All patients will receive 3 cycles of VAD (arm A) or AD (arm B) by rapid infusion.
Patients randomized to arm B will also receive Thalidomide daily, see 9.1.

Agent	Dose/day	Route	Days
Vincristine (only arm A)	0.4 mg	i.v. rapid infusion	1, 2, 3, 4
Doxorubicin	9 mg/m^2	i.v. rapid infusion	1, 2, 3, 4
Dexamethasone	40 mg	p.o.	**All cycles**: 1, 2, 3, 4, 9, 10, 11, 12, 17, 18, 19, 20

Cycle 2 will start at day 29, cycle 3 will start at day 57.
In case a patient receives additional (V)AD cycles these are considered as treatment according to protocol, so the corresponding data will be recorded on the appropriate CRF's.

Assessment of response after cycle 3 is described in paragraph 11 and appendix B.

- All patients who meet the inclusion criteria for CAD and stem cell collection (see 9.3.1) will continue with CAD (see 9.3). This also holds for patients with no response or progressive disease after (V)AD.
- Patients who do not meet the inclusion criteria for mobilization but with a CR, PR or MR are strongly recommended to be treated as described in paragraph 7.6.
- Patients who do not meet the inclusion criteria for mobilization and with no response or with progressive disease will go off protocol treatment.

It should be noted that no response or progressive disease after (V)AD by itself is not a reason to go off protocol treatment.

9.2.1 Special management orders in conjunction with (V)AD.

- It is strongly recommended to give prophylactic treatment for pneumococcus infections and anti-fungal prophylaxis according to local protocols.

9.3 Stem cell mobilization and collection

All eligible patients will be given CAD chemotherapy followed by G-CSF (Neupogen®) for stem cell collection. Patients randomized to arm B will discontinue Thalidomide two weeks before the start of CAD.
CAD will start 4-6 weeks after start of the third (V)AD cycle.

9.3.1 Inclusion criteria for CAD and stem cell collection

- WHO performance 0-3
- Absence of severe pulmonary, neurologic, or psychiatric disease
- Bilirubin and transaminases of less than 2.5 times the upper limit of normal values

9.3.2 Stem cell mobilization with CAD

Agent	Dose/day	Route	Days
Cyclophosphamide	1000 mg/m^2	i.v.	1
Doxorubicin	15 mg/m^2	i.v. rapid infusion	1, 2, 3, 4
Dexamethasone	40 mg	p.o.	1, 2, 3, 4
G-CSF (Neupogen® SingleJect®)	10 µg/kg (divided in 2 gifts daily, according to local rules)	s.c.	day 5 until last pheresis

9.3.3 Special management orders in conjunction with CAD.

- Selective gut decontamination should be performed according to local protocols.

9.3.4 Stem cell collection

Stem cell collection will be performed as soon as CD34$^+$ cells are present in peripheral blood, which is usually between 9-14 days after first day of CAD. In case double intensification is planned (immediately or a second course at relapse) a minimum of 5 x 10^6 CD34$^+$ cells/kg is required. Otherwise 2.5 x 10^6 CD34$^+$ cells/kg are sufficient. In case insufficient stem cells are collected the procedure may be repeated (possibly after the use of cyclophosphamide priming (4000 mg/m^2)) or alternatively bone marrow stem cell collection may be performed.

Assessment of response after stem cell collection is described in paragraph 11 and appendix B.

- All patients who meet the inclusion criteria for intensification (see 9.4.1) will continue with High Dose Melphalan. This also holds for patients with no response or progressive disease after stem cell collection.
- Patients who do not meet the inclusion criteria for intensification but with a CR, PR or MR are strongly recommended to be treated as described in paragraph 7.6.
- Patients who do not meet the inclusion criteria for intensification and with no response or with progressive disease will go off protocol treatment.

It should be noted that no response or progressive disease by itself is not a reason to go off protocol treatment.

9.4 Intensification

All eligible patients will be given High Dose Melphalan between 6 and 8 weeks after stem cell collection.

9.4.1 Inclusion criteria for intensification

- WHO performance 0-2
- Absence of severe pulmonary, neurologic, or psychiatric disease
- Bilirubin and transaminases of less than 2.5 times the upper limit of normal values
- A suitable stem cell graft containing at least 2.5 x 10^6 $CD34^+$ cells/kg

9.4.2 High Dose Melphalan followed by stem cell reinfusion

Agent	Dose/day	Route	Days
Melphalan	100 mg/m²	i.v. rapid infusion	-3, -2*****
Stem cell infusion	2.5 x 10^6 $CD34^+$ cells/kg		0

*** Melphalan 100 mg/m² in patients with renal insufficiency**

Although Melphalan pharmacokinetics are not adversely affected by impaired renal function, the general toxicity of Melphalan 200 mg/m^2 may be increased in patients with a creatinin clearance ≤ 40 ml/min. For patients with a creatinin clearance ≤ 40 ml/min, Melphalan dose should be reduced to 100 mg/m^2, given only at day -3.

Assessment of response after each course of High Dose Melphalan is described in paragraph 11 and appendix B.

- Patients randomized to arm A will continue with α-Interferon maintenance after the last course of HDM (see 9.5), provided they meet the inclusion criteria for IFN maintenance. Otherwise they go off protocol treatment.
- Patients randomized to arm B will continue with Thalidomide maintenance 50 mg/day after the first course of HDM (see 9.1).
- Patients with an HLA-identical family donor may be included in the HOVON 54 trial after the first course of HDM (see 7.7 and 9.7).

9.4.3 Special management orders in conjunction with Melphalan 200 mg/m² (100 mg/m²) and stem cell reinfusion

- A hydration regimen will be started 30 minutes before administration of Melphalan and consists of 500 ml NaCl 0.9 % and 40 mmol KCl over 1 hour. Diuretics must be administered when needed.
- On day 0 the stem cells are thawed at the bedside and infused without washing steps. The procedure will be performed according to the local standard protocols.

9.4.4 Supportive care during Melphalan 200 mg/m² (100 mg/m²) aplasia

- Placement of an indwelling central venous catheter;
- Anovulatory drugs for menstruating females;
- Antibacterial and antifungal prophylaxis;
- Antistreptococcus prophylaxis is recommended from day +4 until day +14.

9.4.5 Second course of Melphalan 200 mg/m^2 followed by stem cell reinfusion

In institutions with a policy of double intensification, the second course of High Dose Melphalan will be administered between 2 and 3 months after the first course. Patients have to meet the criteria as described under 9.4.1 before starting the second course.
The policy of each center should be made clear to the HOVON Data Center before or at the time of registration of the first patient. It is prohibited to follow both policies for different patients in one individual participating center.
Patients that are included in the HOVON 54 trial (see 9.7) wil not receive a second course of HDM, regardless of the center policy. Patients will go off protocol treatment at the time of transplant in the HOVON 54 trial.

9.5 Maintenance therapy with α-Interferon

Patients randomized to arm A who are eligible for maintenance with α-Interferon (Roferon®) will start with IFN maintenance between 2 and 3 months after the last course of HDM. If α-Interferon (Roferon®) has not started within 6 months after HDM, the patient will go off protocol treatment.

9.5.1 Inclusion criteria for α-Interferon maintenance

- WHO performance 0-2
- No progressive disease

- Platelets ≥ 100 x 10^9/l
- WBC ≥ 3 x 10^9/l
- Absence of active infections
- Absence of severe metabolic or psychiatric disease

9.5.2 Administration of α-Interferon

Agent	Dose/day	Route	Days
α-Interferon (Roferon®, preferentially Roferon®-Pen containing 18 x 10^6 IU)	3 x 10^6 IU	s.c.	3 times weekly Stop after progression, or when not at least in PR 3 months after start maintenance

The dose will be 3 x 10^6 IU/day given subcutaneously three times a week.
IFN is continued until progression. IFN is also stopped when a patient has not achieved at least a PR 3 months after start maintenance. When Interferon administration is interrupted for more than 6 weeks, it is regarded as end of maintenance and the patient will go off protocol treatment.

Assessment of response during IFN maintenance is described in paragraph 11 and appendix B.

9.5.3 Dose adjustment of α-Interferon

- Non-hematological toxicity CTC grade 4 and/or leukocytopenia (WBC < 2 x 10^9/l) and/or thrombocytopenia (platelets < 50 x 10^9/l): interrupt IFN. After disappearance of side effects, IFN may be started again at reduced dose levels according to the table below;
- Non-hematological toxicity CTC grade 2 or 3: reduce dose IFN according to the table below.

Dose Reduction Level	Dose/day	Days
Level 1	2 x 10^6 IU	3 times weekly
Level 2	1 x 10^6 IU	3 times weekly
Level 3	1 x 10^6 IU	1 time weekly

When reducing the dose of IFN, start at Dose Reduction Level 1. In case that dose level is still associated with unacceptable side effects, reduce the dose further according to Level 2. If this is insufficient, reduce further to Level 3. In case Level 3 is not tolerated, maintenance therapy is ended and the patient will go off protocol treatment.

9.6 Maintenance therapy with Thalidomide

Patients randomized to arm B will continue with Thalidomide after the first course of HDM. The dose of maintenance Thalidomide is 50 mg daily. For details see paragraph 9.1.
Patients scheduled for inclusion in the HOVON 54 trial, however, should not continue with Thalidomide after the first course of HDM (see 9.7).

9.7 Non-myeloablative allogeneic stem cell transplantation (HOVON 54)

Patients that are scheduled for inclusion in the HOVON 54 trial will be treated according to their allocated treatment arm until 1 HDM course is completed and evaluated.

Arm A: 3 courses of VAD (see 9.2), CAD and stem cell collection (see 9.3), 1 course of HDM and stem cell reinfusion (see 9.4);

Arm B: 3 courses of AD (see 9.2), CAD and stem cell collection (see 9.3), 1 course of HDM and stem cell reinfusion (see 9.4) and Thalidomide (see 9.1);

Patients initially randomized to arm B (Thalidomide) will receive their Thalidomide according to protocol until 2 weeks before CAD. For patients scheduled for inclusion in the HOVON 54 trial, no maintenance therapy (IFN or Thalidomide) will be applied after HDM. If such a patient (for some reason other than disease progression) is not actually included in the HOVON 54 trial, the patient will remain on HOVON 50 protocol treatment. This means maintenance therapy can be started according to the criteria in 9.1 or 9.5.

9.8 Bisphosphonates

It is strongly recommended to start treatment with bisphosphonates at diagnosis and to continue this treatment for at least 2 years. A commonly used regimen consists of pamidronate (APD) 90 mg i.v. once every 4-6 weeks.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. Not eligible for CAD and stem cell collection, and no further treatment with (V)AD
2. Not eligible for intensification with HDM, and no further treatment with (V)AD
3. Not eligible for IFN maintenance
4. Not at least PR 3 months after start IFN maintenance (arm A)
5. Not at least PR 3 months after last course of HDM (arm B)
6. Excessive toxicity (including toxic death)
7. Progression / relapse (not after (V)AD I-III or stem cell collection)
8. Intercurrent death
9. No compliance of the patient (especially refusal to continue treatment)
10. Major protocol violation
11. Completion of protocol treatment (in case of AlloSCT)

11 Required clinical evaluations

Aim of the clinical evaluation at entry is to know in which stage of disease according to Salmon & Durie (see appendix A) the patients are classified and to determine the presence of adverse prognostic factors. Aim of the clinical evaluation during treatment and follow up is to determine response, toxicities and eligibility for further treatment. Evaluation of response is described in paragraph 11.3 and appendix B. Before start of each treatment cycle, routine investigations like blood cell count and renal function will be performed according to local policy.

11.1 Time of clinical evaluations

- At entry: before start of treatment
- After (V)AD III: approximately 3 weeks after start of the third (V)AD cycle
- After (V)AD VI if applicable: approximately 3 weeks after start of the sixth (V)AD cycle
- After stem cell collection: approximately 4 weeks after start CAD
- After each HDM: approximately 6-8 weeks after each course of HDM
- Maintenance and follow up: every 2 months

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

	At entry	After (V)AD III / VI	After stem cell collection	After each HDM	Maintenance and 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				
BM cryopreservation [3)]	X	X		X	X[1)]
Specific investigations					
β_2-microglobulin	X		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.	
Additional investigations	o.i.	o.i.	o.i.	o.i.	o.i.
Cytogenetic analysis	X				

o.i. on indication

1) once a year

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

3) only in institutions that plan to perform molecular analysis

11.2.1 Medical history

Standard medical history, with special attention for:

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

Only at entry:

- Occupational history
- Prior and present other diseases
- Antecedent hematological or oncological diseases
- Previous chemotherapy or radiotherapy
- HLA typing of patient and family

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 each HDM:

- 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

Only ay entry:

- Qualitative serum M-protein
- Qualitative urine M-protein (Bence Jones)

11.2.6 Bone marrow

- Bone marrow biopsy
- Bone marrow aspirate at entry for:
  - Morphology, immunophenotyping
  - Labeling Index (by BRDU) or KI-67
  - Cytogenetic analysis (see 11.2.9)
  - Molecular analysis (cryopreservation, only in institutions that plan to perform molecular analysis like measurement of tumorload with semi-quantitative ASO-PCR)

- Bone marrow aspirate during treatment and follow up for:
  - Morphology
  - Molecular analysis (cryopreservation, only in institutions that plan to perform molecular analysis like measurement of tumorload with semi-quantitative ASO-PCR)

11.2.7 Specific investigations

- 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 idication)

11.2.8 Additional investigations

Only on clinical indication:

- Survey for exclusion of AL amyloidosis
- Bleeding time
- Cryoglobulins, cold agglutins
- Serum viscosity, funduscopy
- Spirometry

11.2.9 Cytogenetic analysis

Conventional cytogenetic analysis should be performed in all patients at diagnosis. Additional FISH analysis for chromosome 13 deletions should also be performed. Conditions for FISH will be standardized by the HOVON Cytogenetic Working Party.

11.3 Evaluation of response

Response will be evaluated according to EBMT, IBMTR and ABMT criteria (see appendix B). Time points are after the third (V)AD course, after the sixth (V)AD course if applicable, after stem cell collection, and after each course of HDM. During maintenance, disease status will be evaluated every 2 months. According to the response criteria a response should be confirmed after 6 weeks. However, in general this can not be applied to the response measurements after (V)AD III, stem cell collection and between the 2 courses of HDM as the treatment intervals are too short.

12 Toxicities

All the chemotherapeutic agents used in the protocol cause pancytopenia and can induce septic or hemorrhagic complications.
Side effects of Thalidomide are constipation, somnolence, neuropathy, rash, weakness and fatigue, which are more frequent with higher doses (400 mg and more). Thalidomide, especially when it is combined with Dexamethasone and Doxorubicin, may increase the risk on Deep Venous Thrombosis (DVT). **DVT is considered a Serious Adverse Event (SAE), and accordingly any DVT must be reported to the HOVON Data Center within 48 hours of the initial observation of DVT** (see paragraph 13).

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

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

1. Event free survival (i.e., time from registration to induction failure, progression or death, whichever occurs first); the time to failure of patients with induction failure is set at one day. Patients are considered induction failure when they have not achieved at least a PR and are not eligible for further treatment according to protocol.

Secondary endpoints

2. Response (PR and CR)
3. Overall survival measured form the time of registration. Patient still alive or lost to follow up are censored at the date they were last known to be alive.
4. Progression free survival (duration of the first response (PR or CR)) measured from the time of achievement of PR (or CR) to date of progression or death from any cause (whichever occurs first).
5. Toxicities of Thalidomide and chemotherapy (according to Appendix C)

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	1	Registration & Randomization Form
2	4	On Study Form
3	2	Cytogenetics Form
4	3	(V)AD Treatment Form
5	3	CAD Mobilization & Stem Cell Collection Form
6	2	HDM & Stem Cell Reinfusion Form
7	2	Thalidomide Maintenance Form
8	2	Interferon Maintenance Form
9	4	Myeloablative Allogeneic Transplantation Form
10	3	Response Evaluation Form
11	1	Off Treatment Form
12	2	Follow Up Form
13	1	Side Effects Form
14	1	Infection Report Form
15	1	General Comments Form
16	1	Prolonged Hypoplasia Form

Table for filling out forms

	Forms															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Registration & randomization	**X**															
On study		**X**	**X**[1]												**(X)**	
Induction Treatment (V)AD				**X**						**X**			**(X)**	**(X)**	**(X)**	
Stem Cell Mobilization					**X**					**X**			**(X)**	**(X)**	**(X)**	
HDM & Stem Cell Reinfusion						**X**				**X**			**(X)**	**(X)**	**(X)**	**(X)**
Thalidomide Maintenance							**X**			**X**					**(X)**	
Interferon Maintenance								**X**		**X**					**(X)**	
Myeloablative Allogeneic Transplantation									**X**	**X**	**X**	**(X)**	**(X)**	**(X)**	**(X)**	**(X)**
End of treatment											**X**	**(X)**			**(X)**	
Follow up										**X**		**X**			**(X)**	

(x) fill out if necessary, see instructions

[1] by local cytogeneticist

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

In order to be able to closely monitor the occurrence of untoward events and detect a difference in failure rate between the two induction treatments (see 17.3) it is of utmost importance that the CRF's regarding induction treatment, especially for the first 100 patients, are sent in in a timely fashion i.e. within one month of completion of the induction treatment.

16 Registration and randomization

16.1 Registration and randomization for induction treatment

The patient should be registered immediately after diagnosis (on the basis of cytological examination of marrow and blood smears in the participating center), and before the start of chemotherapy. Patients need to be registered at the HOVON Data Center of the University Hospital Rotterdam - Daniel 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. Date of diagnosis of multiple myeloma
9. Eligibility criteria
10. Date of start treatment

N.B. Each individual participating center should commit to either one HDM or two HDM in all patients. Every participating center should make this clear to the HOVON Data Center before or at registration of the first patient by that particular center. It is prohibited to follow different policies for different patients in one individual participating center.

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number. Patients will be randomized, stratified by center and treatment policy (one vs. two HDM) with a minimization procedure, ensuring balance within each stratum and overall balance. Patient study number and result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

17 Statistical considerations

17.1 Patient numbers and power considerations

In the previous HOVON 24 MM study we observed the following data:

Accrual rate:	100 patients per year.
EFS at 1, 2 and 3 years from registration:	69%, 43% and 28%.

The target number of patients for this study is 450 to be accrued in 4 years, as in the current study the AZVU will also participate, who expect to enter 10-15 patients per year. After entry of the last patient an additional follow up of 1 year is planned before a first final analysis. It is expected that 5-10% of the patients will receive an allogeneic transplantation; these patients will be censored for EFS at the date of transplantation.
The target number of 450 patients will give a power of 80-82% with a two-sided test at 5% significance level, depending on the number of allogeneic transplantations, to detect an improvement in EFS with hazard ratio HR=0.7, which corresponds with an increase in the EFS at 1 year with 8% to 77% and EFS at 3 years with 13% to 41% in arm B (with Thalidomide).

17.2 Statistical analysis

All analyses will be according the intention to treat principle.

17.2.1 Efficacy analysis

Main endpoint for the comparison of the two induction treatment arms will be EFS from registration as defined in paragraph 14. Secondary endpoints are response rate, overall survival from registration and progression free survival from PR / CR. Actuarial estimates of competing risks of failure (no HDM, progression or death without progression) will be made for each treatment arm. Formal tests for the difference in EFS between the two treatment arms will be done with Cox regression analysis.

17.2.2 Toxicity analysis

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of side effects and infections with CTC grade 2 or more (Appendix C) by treatment arm and cycle. Actuarial competing risks estimates of probability of death will be split by cause of death where a difference will be made between death due to or after relapse or induction failure and death due to side effects of treatment, overall and separately by treatment arm and cycle.

17.2.3 Additional analyses

Additional analyses involve the analysis of prognostic factors, especially β_2-microglobulin and chromosome 13 deletion with respect to response rate, EFS and OS from registration. An exploratory analysis of treatment by factor interactions will also be performed. Logistic and Cox regression analysis will be used for this purpose.

17.3 Interim analyses and safety monitoring

Interim analyses are planned, primarily to guard against unfavourable results in the Thalidomide arm.

Results of the interim analysis will be presented confidentially to an independent data and safety monitoring board (DSMB). Only if the DSMB recommends that the study should be stopped or modified the results will be made public to the principal investigators for further decisions. Interim analyses are planned after 100 and 250 evaluable patients. Before the first interim analysis the response rate and the serious adverse events rate in both treatment arms will be closely monitored in order to pick up any (unexpected) trends. Based on this an earlier first interim analysis may be done.

The main endpoint for the interim analyses is the failure rate. A patient counts as failure if the patients does not achieve a PR on protocol treatment, or if the patient progresses or dies during protocol treatment.

At each interim analysis a detailed report will be generated and presented to the DSMB. The report includes by treatment arm the number of entered patients and at that time evaluable patients, treatment given, the number of failures, actuarial estimates of the different failure types and incidence of SAE's and other side effects and infections (CTC grade).

The DSMB is free in her public recommendations to the study coordinators and the confidential recommendations to the study statistician, but the following guideliness apply:

1. Primary purpose of the interim analyses is to guard against a higher failure rate in the Thalidomide arm compared to the control arm. A higher failure rate in the experimental arm with a P-value < 0.10 is a good reason to recommend the stopping of the trial or recommendations for modifications.
2. A benefit in terms of event free survival or overall survival in the experimental arm is in general no reason to recommend early stopping of the study, unless the associated P-value is very extreme (P < 0.001) and the number of evaluable patients in each arm is at least 100.

17.4 Data and safety monitoring board

A Data and safety monitoring board will be installed before start of the study.

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 randomization. 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
AL	Amyloid Light-chain
ANC	Absolute Neutrophil Count
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	Continuous Infusion
CKTO	`Commissie voor Klinisch Toegepast Onderzoek' (previously "CKVO")
CKVO	`Commissie voor Klinisch Vergelijkend Onderzoek'
CR	Complete Remission
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DCEP	Dexamethasone, Cytosar, Etoposide, Platinum
DSMB	Data and Safety Monitoring Board
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
HB	Hemoglobin
HDM	High Dose Melphalan
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte histocompatibility Antigen
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
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
LVEF	Left Ventricular Ejection Fraction
MCV	Mean Corpuscular Volume
METC	Medical Ethical review committee
MM	Multiple Myeloma
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
PBSC	Peripheral Blood Stem Cell(s)
PD	Progressive Disease
PO	Per Os
PR	Partial Response
SAE	Serious Adverse Event
SC	Subcutaneous
SCT	Stem Cell Transplantation
SD	Stable Disease
TBI	Total Body Irradiation
ULN	Upper Limit of Normal
VAD	Vincristine, Doxorubicin (Adriamycin), Dexamethasone
(V)AD	Induction treatment is VAD in arm A and AD (+Thalidomide) in arm B
VBAP	Vincristine, BCNU, Adriamycin, Prednisone
VMCP	Vincristine, Melphalan, Cyclophosphamide, Prednisone
WHO	World Health Organization
WMO	`Wet Medisch-Wetenschappelijk Onderzoek met mensen'

22 References

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A. Diagnostic Criteria Multiple Myeloma according to Salmon & Durie

DIAGNOSIS OF MULTIPLE MYELOMA

Major criteria:

1. plasmacytoma (tissue biopsy)
2. > 30% plasma cells in bone marrow
3. monoclonal serum M-protein IgG > 35 g/l; IgA >20 g/l, or urine M-protein >1 g/24 hrs in the absence of amyloidosis

Minor criteria:

a. plasma cells in bone marrow > 10% but ≤ 30%

b. monoclonal serum M-protein IgG ≤ 35 g/l, IgA ≤ 20 g/l, urine M-protein ≤ 1 g/24 hrs

c. lytic bone lesions

d. normal IgG <6 g/l **or** IgM <0.5 g/l **or** IgA <0.2 g/l

Multiple Myeloma is diagnosed in case one of the following combinations of criteria is present:

1 + b **or** 1 + c **or** 1 + d

2 + b **or** 2 + c **or** 2 + d

3 + a **or** 3 + c **or** 3 + d

a + b + c **or** a + b + d

STAGING OF MULTIPLE MYELOMA

Stage I	Low Tumor Mass – all of the following:
	Hemoglobin > 6.2 mmol/l
	Ca^{2+} < 2.65 mmol/l *
	IgG < 50 g/l
	IgA < 30 g/l
	Urine M-protein < 4 g/24 hrs
	Normal skeletal assessment or solitary plasmacytoma
Stage II	Intermediate Tumor Mass:
	Patients who qualify for neither Stage I nor III
Stage III	High Tumor Mass – Any one of the following:
	Hemoglobin < 5.3 mmol/l
	Ca^{2+} > 2.65 mmol/l *
	IgG > 70 g/l
	IgA > 50 g/l
	Urine M-protein > 12 g/24 hrs
	≥ 3 lytic bone lesions on skeletal survey (bone scans are not acceptable)
A	Normal renal function (creatinin < 177 μmol/l)
B	Renal insufficiency (creatinin ≥ 177 μmol/l)

* Correct the serum Ca^{2+} by adding 0.02 mmol/l for every g/l albumin below 40 g/l

B. 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.

C. 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.

D. 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

E. 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

F. Patiënteninformatie

Patiënten-informatie behorende bij de studie: Een gerandomiseerde fase III studie naar het effect van Thalidomide gecombineerd met Adriamycine, Dexamethasone (AD) en Hoge Dosis Melfalan bij patienten met Multipel Myeloom.

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 bent gevraagd deel te nemen aan een 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.

Wat is multipel myeloom: De aandoening wordt veroorzaakt door een woekering van abnormale cellen (plasmacellen) in het beenmerg. Bekende ziektesymptomen zijn botpijn, spontane botbreuken en korter worden door botaantasting, moeheidsverschijnselen door bloedarmoede en verhoogde gevoeligheid voor infecties door een gestoorde afweer. Deze symptomen zijn lang niet altijd bij iedereen aanwezig en soms zelfs wordt de ziekte bij toeval ontdekt bij iemand die vrijwel geen klachten heeft. Deze verscheidenheid in presentatie en aanwezigheid van de symptomen heeft niet alleen te maken met het stadium waarin de ziekte zich bevindt op moment van het stellen van de diagnose (beginstadium of al een verder gevorderd stadium) maar ook met het al of niet aanwezig zijn van extra ongunstige factoren. Hierop zal nader worden ingegaan onder het hoofdstuk Onderzoek voorafgaand aan de behandeling (zie onder).

De huidige behandeling: In de laatste jaren is onderzocht of een intensievere behandeling, met hoge dosis chemotherapie al of niet gecombineerd met totale lichaamsbestraling en soms

ondersteund met een stamcel transplantatie, de vooruitzichten van de patiënt met multipel myeloom verbetert. (Bij een allogene stamceltransplantatie worden bloed- of beenmergstamcellen van een donor gebruikt; in het algemeen is dat een familiedonor. Bij een autologe stamceltransplantatie worden eigen stamcellen gebruikt. Hoe deze stamcellen worden verkregen en hoe een (autologe) stamceltransplantatie wordt uitgevoerd, wordt hieronder in detail beschreven.) Na de intensieve behandeling wordt in het algemeen onderhoudstherapie met Interferon gegeven om het terugkomen van de ziekte tegen te gaan (zie onder). Gebleken is dat een groter percentage van de patiënten positief op de intensieve behandeling reageert (in vergelijking tot de minder intensieve therapie) en dat bij hen die goed reageren de ziekte langdurig (meerdere jaren) onder controle kan komen. Helaas is het wel zo dat ook na een zeer goede reactie op de behandeling de ziekte vrijwel altijd weer terugkomt en dat het multipel myeloom vooralsnog als een ongeneeslijke aandoening moet worden beschouwd.

Behandeling met Thalidomide. Thalidomide, vroeger als Softenon voorgeschreven als slaapmiddel, werd in de zestiger jaren uit de handel genomen omdat het misvormingen veroorzaakte bij ongeboren kinderen. Onlangs werd ontdekt dat Thalidomide effectief kan zijn bij de behandeling van het multipel myeloom. Bij ongeveer 30% van de patiënten die op geen enkele vorm van behandeling meer reageerden bleek Thalidomide alsnog een gunstig effect te hebben. Omdat Thalidomide veel hoger werd gedoseerd dan gebruikelijk was, hadden de meeste patiënten milde tot ernstige bijverschijnselen zoals sufheid, obstipatie en soms heftige zenuwpijnen. Ook geeft Thalidomide behandeling een verhoogde kans op thrombose, vooral wanneer het gecombineerd wordt met bepaalde cytostatica (= anti-kanker medicijnen). Om deze reden krijgen patiënten tijdens de behandeling met Thalidomide in combinatie met chemotherapie soms uit voorzorg medicijnen tegen thrombose voorgeschreven.
Het werkingsmechanisme van Thalidomide bij het multipel myeloom is nog niet precies bekend. Het remt waarschijnlijk de vorming van bloedvaatjes waardoor de tumor cellen in het beenmerg onvoldoende “gevoed” worden en daardoor afsterven. Thalidomide werkt in ieder geval heel anders dan de gebruikelijke cytostatica (chemotherapie).
Er is nog vrijwel niets bekend over de toepassing van Thalidomide al of niet in combinatie met chemotherapie bij onbehandelde patiënten en of dit een gunstig verloop op de ziekte kan hebben.

Doel en achtergrond van het onderzoek

Het doel van het onderzoek is om:

1. De effectiviteit van de gecombineerde behandeling van lage dosis Thalidomide met intensieve therapie te vergelijken met de behandeling met intensieve therapie alleen.
2. Te bepalen wat de bijwerkingen van deze behandelingen zijn.
3. Vast te stellen bij welke patiënten toevoeging van Thalidomide aan de intensieve therapie eventueel *wel* en bij welke patiënten toevoeging *niet* zinvol is.

Om een objectieve vergelijking te kunnen maken zal het lot bepalen voor welke behandeling u in aanmerking komt: intensieve therapie *alleen* of intensieve therapie *gecombineerd met* Thalidomide. De loting zal verricht worden voordat met de behandeling wordt begonnen. Mocht u niet aan het onderzoek mee willen doen, dan zal u de standaard behandeling (intensieve therapie alleen, gevolgd door onderhoudstherapie met Interferon) worden aangeboden.

Behandelingsplan

Na uitgebreid onderzoek vooraf (zie onder Onderzoek voorafgaand aan de behandeling) volgt de behandeling die in 4 fasen plaats vindt. In de eerste fase worden 3 chemotherapie behandelingen volgens het VAD schema gegeven, als u voor de standaardbehandeling hebt geloot en 3 chemotherapie behandelingen volgens het AD schema als u voor de behandeling hebt geloot die gecombineerd wordt met Thalidomide. Hieronder zullen deze behandelingen worden uitgelegd. Als u voor de Thalidomide behandeling hebt geloot zult u tevens tijdens de eerste fase van de behandeling anti-thrombose medicijnen voorgeschreven krijgen. In de tweede fase worden uit uw bloed beenmergstamcellen geoogst en ingevroren na voorbehandeling met het zgn. CAD schema (zie onder). Deze worden later gebruikt ter ondersteuning van de intensieve behandeling. In de derde fase van de behandeling vindt de intensieve behandeling met hoge dosis chemotherapie gevolgd door stamceltransplantatie plaats. Voor de intensieve behandeling wordt u enkele weken (3-4 weken) in het ziekenhuis opgenomen. In de vierde fase van de behandeling wordt onderhoudsbehandeling gegeven met als doel het terugkomen van de ziekte tegen te gaan dan wel uit te stellen. Als u voor de Thalidomide behandeling hebt geloot dan zult u ook na het afsluiten van de intensieve behandeling doorgaan met dagelijks Thalidomide in te nemen. In het andere geval wordt u Interferon voorgeschreven.

Onderzoek voorafgaand aan de behandeling.

Het onderzoek is erop gericht om na te gaan in welk stadium uw ziekte zich bevindt, in hoeverre er geen belemmeringen bij u aanwezig zijn de behandeling uit te voeren en om na te gaan of uw ziekte extra ongunstige kenmerken heeft. Naast routine bloed en urine onderzoek zullen er röntgenfoto's van uw skelet gemaakt worden en zal uw beenmerg onderzocht worden. Vooral het beenmergonderzoek is van groot belang . Hiermee kunnen de eigenschappen van de kwaadaardige tumor cellen onderzocht worden, zodat bepaald kan worden of er bij u extra ongunstige factoren aanwezig zijn.

Eerste fase: VAD of AD kuren

Als u voor de standaard behandeling hebt geloot krijgt u de zgn. VAD kuren. VAD is een afkorting van de geneesmiddelen vincristine, adriamycine en dexamethason. Vincristine en Adriamycine krijgt u via een kortlopend infuus op 4 achtereenvolgende dagen. Dexamethason is een vorm van prednison. Dit middel wordt in tabletvorm gegeven gedurende de eerste 4 dagen van de kuur tegelijkertijd met het infuus en daarna nog 2 keer gedurende 4 dagen met een onderbreking van 4 dagen. U krijgt dus dexamethason op dag 1-4, 9-12 en op dag 17-20 van de kuur. De kuur wordt 1 x per maand gegeven. Het VAD schema wordt in het algemeen goed verdragen. De bijwerkingen die optreden zijn meestal het gevolg van de dexamethason en kunnen bestaan uit maagklachten, slapeloosheid en opgewondenheid. Wel is er een grote kans dat uw haar uitvalt. Na afloop van de gehele behandeling komt het haar weer terug. Soms treden tintelingen, prikkelingen en een doof gevoel aan uw vingertoppen of tenen op. Dit is een bijwerking van de vincristine als gevolg van stoornissen in de zenuwgeleiding (zgn polyneuropathie). Dit kan een reden zijn om de dosering van de vincristine te verminderen of zelfs om de vincristine geheel weg te laten. De polyneuropathie klachten verdwijnen in het algemeen helemaal mits de vincristine behandeling op tijd wordt aangepast. Omdat Thalidomide ook polyneuropathie klachten kan geven wordt, als u voor de Thalidomide behandeling hebt geloot, géén vincristine gegeven. Dit om de kans op ernstige bijwerkingen (polyneuropathie) te voorkomen. U krijgt dus AD kuren als u voor de Thalidomide arm hebt geloot. De VAD en AD kuren worden poliklinisch gegeven gedurende 3 maanden 1 maal per maand.

Behandeling met Fraxiparine ter voorkoming van thrombose

Onlangs is bekend geworden dat Thalidomide een verhoogde kans op thrombose geeft, vooral als het wordt gecombineerd met adriamycine en dexamethason, medicijnen die u tijdens de eerste twee fasen van de behandeling zult gebruiken. De oorzaak hiervan is niet bekend. Als u voor de Thalidomide arm hebt geloot wordt u het anti-thrombose medicijn "Fraxiparine" voorgeschreven.

Dit medicijn word gebruikt bij de behandeling maar ook ter voorkoming van thrombose. Bij de behandeling van thrombose wordt het in het algemeen 2 x daags toegediend. Als preventie medicijn wordt het 1 x daags voorgeschreven (in een lagere dosis dan wordt toegepast bij de behandeling van thrombose). De Fraxiparine wordt door u zelf of als u dat niet wilt, door iemand uit uw omgeving 1 x daags onder de huid gespoten. De Fraxiparine wordt gedurende de gehele eerste fase van de behandeling voorgeschreven en gestopt 1 week voor start van de CAD kuur. De Thalidomide is dan al gestopt en wordt pas weer hervat na de eerste Melfalan kuur. Omdat dan een veel lagere dosis Thalidomide (50 mg) wordt voorgeschreven en van de combinatie Melfalan en Thalidomide geen verhoogd thrombose risico bekend is, krijgt u dan ook geen thrombose preventie meer voorgeschreven.
De verwachting is dat met deze maatregelen het risico op thrombose minder is. Het is echter niet uitgesloten dat ondanks deze maatregelen bij u toch thrombose optreedt. De verschijnselen hiervan kunnen zijn een gezwollen, pijnlijk, warm en rood been, maar ook plotseling optredende kortademigheid en/of pijn op de borst. Mochten deze symptomen bij u ontstaan dan dient u onmiddellijk contact met uw specialist of diens vervanger op te nemen.
Bij ontstaan van thrombose zal de Thalidomide behandeling bij u gestopt worden. Uw behandelend arts zal met u bespreken of in een latere fase van de behandeling de Thalidomide weer hervat zal worden. Het streven zal zijn de overige behandeling volgens oorspronkelijk plan voort te zetten.
Bijwerkingen van de Fraxiparine kunnen zijn (onschuldige) huidbloedinkjes op de plek van de injecties. De kans op ernstige bloedingen is vrijwel nihil, tenzij er bij u al een sterk verhoogde bloedingsneiging bestaat. Uw specialist zal u hier zonodig op onderzoeken.

Tweede fase: CAD behandeling en stamcelverzameling

Vier weken tot zes weken na de derde AD kuur zult u behandeld gaan worden met een CAD kuur. De C staat voor het cytostaticum Cyclophosphamide. Cyclophosphamide wordt op de eerste dag van de kuur op de polikliniek toegediend door middel van een snel lopend infuus. De Adriamycine en Dexamethason zullen evenals in het AD schema en op dezelfde wijze op de eerste 4 dagen dag van de kuur worden toegediend. Op de vijfde dag van de kuur start de behandeling met de beenmergstimulerende factor “G-CSF“. Dit middel stimuleert de aanmaak van beenmerg stamcellen. Na een aantal dagen verschijnen deze stamcellen in het bloed en kunnen dan hieruit worden “geoogst” (stamcel ferese, zie hieronder voor verdere uitleg). G-CSF kunt u zelf spuiten, eventueel kan dit ook door uw partner, een wijkverpleegkundige of de huisarts. De verpleging zal u hiertoe instructies geven. G-CSF geeft weinig bijwerkingen. Soms treedt er spierpijn of botpijn (b.v. lage rugpijn) op die geheel verdwijnt na het staken van het gebruik van het medicament.

Op het moment dat er stamcellen in het bloed verschijnen, meestal rond de 10e dag na het begin van G-CSF toediening, zullen deze uit het bloed worden verzameld. Het juiste moment van de stamcel verzameling wordt door bloedonderzoek (meting van stamcellen) vastgesteld. De bloedcellen worden middels een zogenaamde 'stamcel ferese' verzameld. Daarbij wordt het bloed na aanprikken van twee bloedvaten via een slangetje buiten het lichaam door een machine gevoerd. U kunt dit vergelijken met nierdialyse. In deze machine wordt het bloed gecentrifugeerd. De witte bloedcellen met de stamcellen worden uit het bloed gehaald en opgevangen, de rest van het bloed krijgt u weer terug. U ligt gedurende 3 tot 4 uur aan de machine. Om voldoende stamcellen uit het bloed te oogsten voor de transplantaties moet de stamcel ferese soms de volgende dag herhaald worden. De geoogste bloedstamcellen worden ingevroren totdat ze worden toegediend.

<u>De intensieve behandeling met autologe stamceltransplantatie</u>

Voorafgaand aan de opname worden enkele onderzoeken verricht: bloedonderzoek, röntgenfoto's en kweken, met de bedoeling infectiebronnen op te sporen en eventueel te behandelen. U wordt opgenomen op de verpleegafdeling voor behandeling met de zgn. *<u>H</u>oge <u>D</u>osis <u>M</u>elfalan*. Het doel is om met deze hoge dosis chemotherapie zoveel mogelijk (resterende) kwaadaardige plasma cellen uit te schakelen. Omdat door de intensieve behandeling ook het normale beenmerg volledig uitgeschakeld wordt, moet deze behandeling ondersteund worden door een stamceltransplantatie. Hiervoor worden de stam cellen gebruikt die bij u in een eerdere fase zijn afgenomen en ingevroren.

Allereerst ontvangt u een speciaal toedieningssysteem, een zogeheten Hickman of subclavia catheter. Onder plaatselijke verdoving wordt via een klein sneetje onder het sleutelbeen een catheter (=slangetje) ingebracht. Door deze catheter, die gehele opname blijft zitten, kunnen infusen gegeven worden en kan bloed worden afgenomen voor onderzoek. Daarna kan de intensieve behandeling beginnen. De chemotherapie (Melfalan) wordt gedurende 2 tot 3 uur op twee opeenvolgende dagen met een infuus via deze catheter toegediend.

Enkele dagen na het Melfalan-infuus ontvangt u uw eigen ontdooide stamcellen weer terug. Deze worden ook via de Hickman of subclavia catheter toegediend. De stamcellen weten via de bloedbaan hun plek in het beenmerg weer te vinden. Het duurt ongeveer 2 weken voordat de bloedaanmaak (na de Melfalan) weer op gang komt. In deze periode zult u dan ook transfusies van rode bloedlichaampjes en van bloedplaatjes ontvangen. Ook bestaat er in deze periode gevaar voor infecties, die zonodig met antibiotica worden behandeld. Andere bijwerkingen die kunnen optreden zijn misselijkheid, braken en slijmvlies beschadigingen. Deze bijwerkingen zullen zo goed

mogelijk met medicijnen worden bestreden. Het is vrijwel zeker dat u tijdelijk volledig kaal wordt. De totale opname zal drie tot vijf weken duren. In deze periode ligt u op een één- of tweepersoonskamer.

Tweede intensieve behandeling

Enkele ziekenhuizen hebben er voor gekozen de intensieve behandeling een tweede keer te geven, 2 tot 3 maanden na de eerste intensieve behandeling. Dit is gebaseerd op de voorlopige resultaten van nog lopende studies waarbij werd vastgesteld dat door een dubbele intensieve behandeling een klein percentage van de patiënten langere overlevings kansen zouden verkrijgen. In andere studies werd er echter geen verschil gevonden tussen enkel of dubbel intensieve behandeling, zodat op dit moment niet duidelijk is wat de beste benadering is. Mocht u in een ziekenhuis behandeld worden dat voor een enkele intensieve behandeling heeft gekozen dan zullen er in ieder geval voldoende stam cellen worden ingevroren om bij het eventueel terugkomen van de ziekte alsnog een tweede intensieve behandeling te kunnen geven.

Onderhoudsbehandeling met Interferon of Thalidomide

Interferon is een eiwitachtige stof, dat onder bepaalde omstandigheden in het lichaam wordt geproduceerd en onder andere een rol speelt bij ontstekingsprocessen, maar ook betrokken is bij de tumorafweer. Men is nu in staat het Interferon in zuivere vorm in grote hoeveelheden in het laboratorium te produceren. Interferon wordt veelvuldig toegepast als onderhoudstherapie bij multipel myeloom patiënten die goed op een voorafgaande behandeling met cytostatica hebben gereageerd met als doel het terugkomen van de ziekte tegen te gaan. Het Interferon wordt door u zelf of als u dat niet wilt, door iemand uit uw omgeving, 3 x per week onder de huid gespoten, op dezelfde manier zoals patiënten met suikerziekte zichzelf behandelen met insuline injecties. Bekende bijwerkingen van Interferon zijn griepachtige verschijnselen, zoals koorts, rillerigheid spierpijn, gewrichtsklachten en moeheid. Deze treden vooral in het begin van de behandeling op en kunnen vaak goed onderdrukt worden door paracetamol. In het verloop van de behandeling verdwijnen de bijwerkingen vaak weer. Interferon behandeling start 2 tot 3 maanden na de intensieve behandeling. Als u voor de Thalidomide hebt geloot wordt Thalidomide na de intensieve behandeling als onderhoudsbehandeling voortgezet. De onderhoudsdosering van Thalidomide is lager dan de dosering die werd voorgeschreven tijdens de chemotherapie fase (50 mg Thalidomide ipv. 200 mg). Dit om de kans op ernstige bijwerkingen tgv. het langdurig gebruik van Thalidomide te verkleinen. De onderhoudsbehandeling wordt voortgezet totdat de ziekte eventueel weer terugkomt of eerder als er onacceptabele bijwerkingen optreden.

Aanvullende donor stamceltransplantatie

In een aantal ziekenhuizen in Nederland loopt een onderzoek naar de waarde van de zogenaamde “Niet myeloablatieve donor stamceltransplantatie” (minitransplantatie, HOVON 54 protocol) in aansluiting (2-4 maanden nà) de intensieve behandeling met HDM. Deze transplantatie kan alleen worden uitgevoerd als u een “identieke” broer of zuster mocht hebben. Dit kan door middel van een bloedtest bepaald worden. Mocht uw ziekenhuis aan dit onderzoek meedoen, dan zal u hierover apart worden ingelicht via uw behandelend arts en de schriftelijke patiënteninformatie van de HOVON 54 studie.

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 stamcel transplantatie en vervolgens een beenmergpunktie 1x per jaar. Ook zal het röntgenonderzoek van het skelet 1x per jaar herhaald worden.

Extra belasting door deelname aan de studie:

Ook patiënten die de standaard behandeling ondergaan worden nauwkeurig onderzocht op de uitbreiding van het ziektebeeld inclusief beenmergonderzoek en röntgenonderzoek. Dit gebeurt zowel bij diagnose en tijdens het verloop van de behandeling. In essentie zijn er geen extra onderzoeken verbonden aan de intensieve behandeling met Thalidomide. Wel kan Thalidomide bepaalde bijwerkingen hebben. Omdat de gekozen dosering van Thalidomide veel lager is dan tot nog toe gebruikt is bij patiënten, is de verwachting dat u in uw functioneren niet of nauwelijks zal worden belemmerd door gebruik van dit medicament. De mogelijke bijwerkingen van Thalidomide worden hieronder apart besproken. Hoewel autologe stamceltransplantatie inmiddels een routine procedure is geworden en al bij duizenden patiënten met verschillende kwaardaardige aandoeningen is uitgevoerd kunnen er toch fatale complicaties optreden door de transplantatie zoals onbehandelbare infecties, bloedingen, long- en leverstoornissen. De ervaring tot nog toe laat zien dat ongeveer 5% van de patienten overlijdt als gevolg van onbehandelbare bijwerkingen van de behandeling.

Bijwerkingen van de chemotherapie

Een van de bijwerkingen van de intensieve behandeling met hoge dosis Melfalan willen we hier apart vermelden: Er is een grote kans dat u na de intensieve behandeling niet meer vruchtbaar bent. Dit is na afsluiting van de behandeling met meer zekerheid vast te stellen door middel van

een bloedonderzoek als u vrouw bent en door middel van zaad (sperma) onderzoek als u man bent. Hebben u en uw partner nog kinderwens dan raden wij u aan dit eerst met elkaar en vervolgens met uw behandelend arts te bespreken. Mogelijk kan dit een reden zijn dat u niet aan deze studie wilt deelnemen. Desgewenst kan wel sperma voordat de behandeling begint worden ingevroren voor later.
Nadere informatie over algemene bijwerkingen van chemotherapie kunt u vinden in de folder over chemotherapie van het Koningin Wilhelmina Fonds (Nederlandse Kankerbestrijding).

Bijwerkingen van de Thalidomide

De meest bekende bijwerkingen zijn sufheid en slaperigheid overdag, obstipatie en pijnscheuten, tintelingen, prikkelingen en doofheid in vingertoppen en tenen (polyneuropathie). Deze bijwerkingen treden vooral op bij hoge doseringen (400 mg of meer per dag) welke langdurig worden gebruikt. Om de kans op bijwerkingen zo klein mogelijk te maken is de start dosering van Thalidomide 200 mg per dag en alleen als u geen of vrijwel geen bijwerkingen hiervan ondervindt, zal de dosering eventueel door uw behandelend arts verhoogd worden tot maximaal 400 mg per dag. De dosering van 200 tot eventueel 400 mg wordt u alleen tijdens de eerste 3 maanden van de behandeling (tijdens de AD kuren) voorgeschreven. Als onderhoudstherapie (deze start direct na de eerste Hoge Dosis Melfalan) neemt u dagelijks 50 mg Thalidomide. Uit andere onderzoeken is gebleken dat ook deze lage doseringen van Thalidomide effectief kunnen zijn bij het multipel myeloom. Zoals u al hebt kunnen lezen, is onlangs bekend geworden dat Thalidomide een verhoogde kans op thrombose geeft, vooral als het wordt gecombineerd met dexamethason en adriamycine. Nog niet bekend is wat de oorzaak hiervan is. Uit voorzorg krijgt u dan ook Fraxiparine voorgeschreven tijdens de eerste fase (AD kuren) van de behandeling.
Als u ernstige bijwerkingen van de Thalidomide ondervindt zal de dosering verlaagd worden eventueel na een korte periode van onderbreking of mogelijk zal zelfs de Thalidomide geheel gestopt worden.
Zoals hierboven al is vermeld kan Thalidomide misvormingen geven bij ongeboren kinderen. Het is dan ook noodzakelijk dat u adequate anti-conceptie gebruikt.

Niet alle mogelijke bijwerkingen zijn hierbij vermeld. Het is ook niet zo dat alle genoemde bijwerkingen met zekerheid bij elke patiënt zullen optreden. Bij het optreden van onbegrepen klachten of verschijnselen is het aangewezen om te overleggen met Uw behandelend arts.

Opslag van bloed en beenmerg materiaal:

Als u er geen bezwaar tegen hebt zal bij u voor start van de behandeling, na de laatste VAD of TAD kuur en 2-3 maanden na afsluiting van de Hoge Dosis Melfalan kuur (kuren) bloed (per keer $\pm$ 10 ml) worden afgenomen en bewaard. Dit wordt gedaan om mogelijk later vast te kunnen stellen welke patiënten een verhoogd risico voor thrombose hebben. Ook zal als u er geen bezwaar tegen hebt een deel van het beenmerg dat eventueel overblijft nadat hierop de benodigde diagnostiek is verricht, bewaard blijven in vloeibare stikstof. Dit wordt gedaan om eventueel later nog aanvullend onderzoek te kunnen verrichten. Hierbij kan mogelijk worden vastgesteld welke patiënten wel of geen baat hebben bij intensieve behandeling gecombineerd met Thalidomide. Als u hier wel bezwaar tegen hebt wordt het eventueel overblijvende beenmergmateriaal vernietigd.

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. Dit zal geen consequenties hebben voor uw verdere behandeling noch voor de relatie met uw arts. Uw gegevens worden anoniem verwerkt. Mocht u verdere vragen hebben kunt u altijd contact opnemen met ondergetekenden of met de andere artsen van de afdeling Hematologie. Uw huisarts zal van uw eventuele deelname aan de studie op de hoogte worden gebracht.

Voor- en nadelen

Als u aan de studie mee doet en u voor de “experimentele” arm in aanmerking komt (de gecombineerde behandeling met Thalidomide), reageert u mogelijk beter op de behandeling en duurt het mogelijk ook langer voordat de ziekte terug komt. Krijgt u Thalidomide dan is het zeker niet uitgesloten dat er extra bijwerkingen optreden zoals sufheid overdag, obstipatie en zenuwpijnen, bijwerkingen die niet aanwezig zijn als u de standaard behandeling zonder Thalidomide krijgt. 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

Het is, zoals gezegd, niet precies bekend welke van de twee behandelingen de beste is. Daarom heeft uw arts 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, zal u de gebruikelijke “standaard”-behandeling voorgesteld worden. 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 Patientenservice. Patientenservice 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.

*Bijlagen: (Nederlandse Kankerbestrijding)

- Folder Wetenschappelijk onderzoek bij patiënten met kanker (Nederlandse Kankerbestrijding)
- Folder *De ziekte van Kahler* (Nederlandse Kankerbestrijding)
- Folder Instituut voor Gezondheidsethiek

TOESTEMMINGSVERKLARING
voor deelname aan het wetenschappelijk onderzoek:

Een gerandomiseerde fase III studie naar het effect van Thalidomide gecombineerd met Adriamycine, Dexamethasone (AD) en Hoge Dosis Melfalan bij patienten met Multipel Myeloom.

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: .....

Ik heb geen / wel bezwaar tegen het opslaan van mijn bloed voor wetenschappelijk onderzoek.

Ik heb geen / wel bezwaar tegen het opslaan van mijn beenmerg voor wetenschappelijk onderzoek.

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.

G. Factor VIII and von Willebrand factor as a risk factor for Thalidomide induced Deep Venous Thrombosis in Multiple Myeloma

Introduction:

In about 5-10% of the patients with multiple myeloma who received VAD chemotherapy, Deep Venous Thrombosis (DVT) has been observed. In the HOVON 24 MM-study with 441 eligible patients, DVT was reported in 22 patients (5%).

Thalidomide has a strong prothrombogenic action. When Thalidomide is combined with chemotherapy an incidence of 25% of DVT has been observed.[1] For this reason, all patients randomized to the Thalidomide arm in the HOVON 50 MM study, will receive prophylaxis with low dose, low molecular heparin during induction therapy with AD + Thalidomide (TAD).

The mechanism sofar is unknown. A study performed in the department of Hematology, University Medical Center, Utrecht, showed that plasma factor VIII (FVIII) levels in myeloma are highly elevated. In a group of 57 patients the median FVIII concentration was 300%. Especially patients with a high tumor load and active myeloma have high levels. Other procoagulant factors tested, including FXI, fibrinogen, APC resistance and anti-coagulant factors like ATIII, prot C/S, TFPI, were not abnormal. Also fibrinolysis was not disturbed. Other studies have shown that FVIII is an independent risk factor for DVT.[2]

Increased FVIII levels are probably a reflection of increased angiogenesis in myeloma foci. In these foci, endothelial cells produce high levels of von Willebrand factor (vWF) to which FVIII is coupled. In accordance with this assumption is our preliminary observation that FVIII and vWF levels decrease after successful tumor reduction by chemotherapy and/or anti-angiogenesis therapy.

References:

1. Zangari M, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving Thalidomide and chemotherapy. Blood 98: 1614-1615, 2001
2. Kyrle PA, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med. 343: 457-462, 2000

Study objectives:

- To investigate the association between FVIII/vWF levels and incidence of DVT in patients who receive TAD combined with heparin prophylaxis. This will also be done in patients who receive VAD without Thalidomide;
- To investigate the association between FVIII/vWF levels and tumor load;

- To investigate the association between FVIII/vWF levels and response after VAD/TAD or HDM;
- To evaluate the prognostic value of high FVIII/vWF levels with respect to survival endpoints.

Design:

Evaluation of FVIII/vWF at diagnosis, after VAD/TAD and HDM, and in case of DVT.

Blood sampling and storage: Citrate plasma 5-6 ml, divided over 2 tubes **(all patients).**

sample 1 : before start of therapy

sample 2 : 4 weeks after last VAD/TAD

sample 3 : 3 months after last HDM

extra : in case of DVT

Storage:

-80 °C (code: HOVON 50 patient study number + date sample, in own institute or in reference center).

Performance of tests:

To exclude interlaboratory variation all tests will be performed in one center (UMCU), after collection of the samples. Preferably collected samples will be sent out **(deep frozen!)** to the reference lab UMCU after notifying one of the UMCU coordinators.

Address:

UMCU
Laboratorium voor Speciele Hematologie, HP G03647
Heidelberglaan 100
3584 CX Utrecht, The Netherlands.

Statistical considerations:

The main end point will be the comparison of the incidence rate of DVT in patients with low vs high FVIII/vWF levels. It is assumed that DVT will occur during or after VAD in about 10% of the patients in the treatment arm without Thalidomide. The incidence of DVT in patients who receive AD + Thalidomide but without heparin prophylaxis is about 25%; the efficacy of prophylaxis with heparin however is unknown.

When the incidence of DVT in patients who receive AD + Thalidomide will be reduced to 10% due to the heparin prophylaxis, then the overall incidence of DVT will be about 10% in this study. However, when heparin has no significant effect on the occurrence of DVT, then the overall

incidence will be about 15%. For both situations we can calculate the sample size necessary to detect a difference in incidence rate of DVT in patients with low vs high levels of FVIII or vWF. Therefore we will divide patients into two equal groups based on the measured levels (low vs high). First we assume that DVT will occur in 10% of the patients. Then the incidence *p1* will be *0.10-x* in patients with low FVIII and the incidence *p2* will be *0.10+x* in patients with high levels. In order to have a power 1 - β = 0.80 to detect a difference *p2-p1* using a two-sided significance level α = 0.05, *n* patients are needed in each of the two groups. The table below specifies for several combinations the total number of patients *(N = n + n)* needed.

x	p1=0.10-x	p2=0.10+x	N = n1 + n2
0.04	0.06	0.14	488
0.05	0.05	0.15	320
0.06	0.04	0.16	226
0.08	0.02	0.18	132

When the overall incidence of DVT would be 15% instead, then the incidence *p1* will be *0.15-x* in patients with low FVIII and the incidence *p2* will be *0.15+x* in patients with high levels. This would require the following number of patients:

x	p1=0.15-x	p2=0.15+x	N = n1 + n2
0.05	0.10	0.20	438
0.07	0.08	0.22	230
0.08	0.07	0.23	180

The effect of FVIII/vWF levels on the incidence of DVT will be evaluated with FVIII/vWF divided into two groups (low vs high), but also as a continuous variable. The analyses will be stratified by treatment arm.

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