Autologous stem cell transplantation for patients with AL amyloidosis

A prospective phase II study.

PROTOCOL

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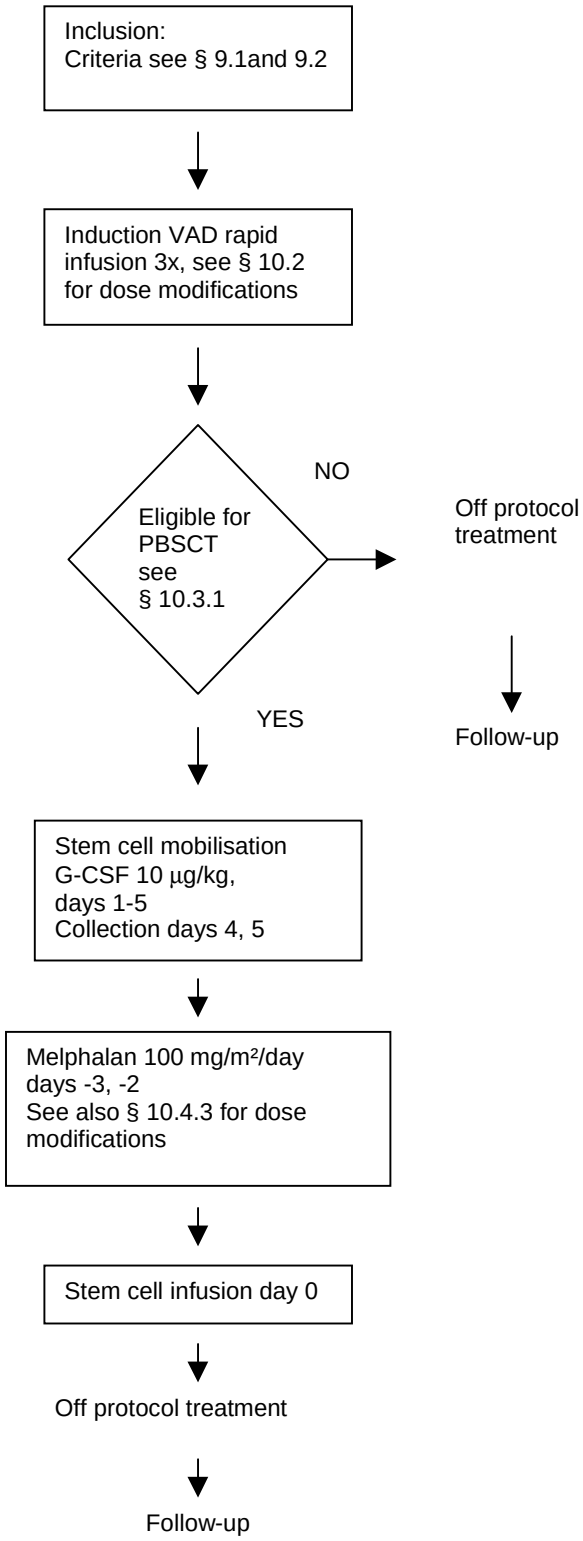
First version : 1999
Version : 1 September 2000
Date of activation : 4 September 2000

CKVO number : 2000-03

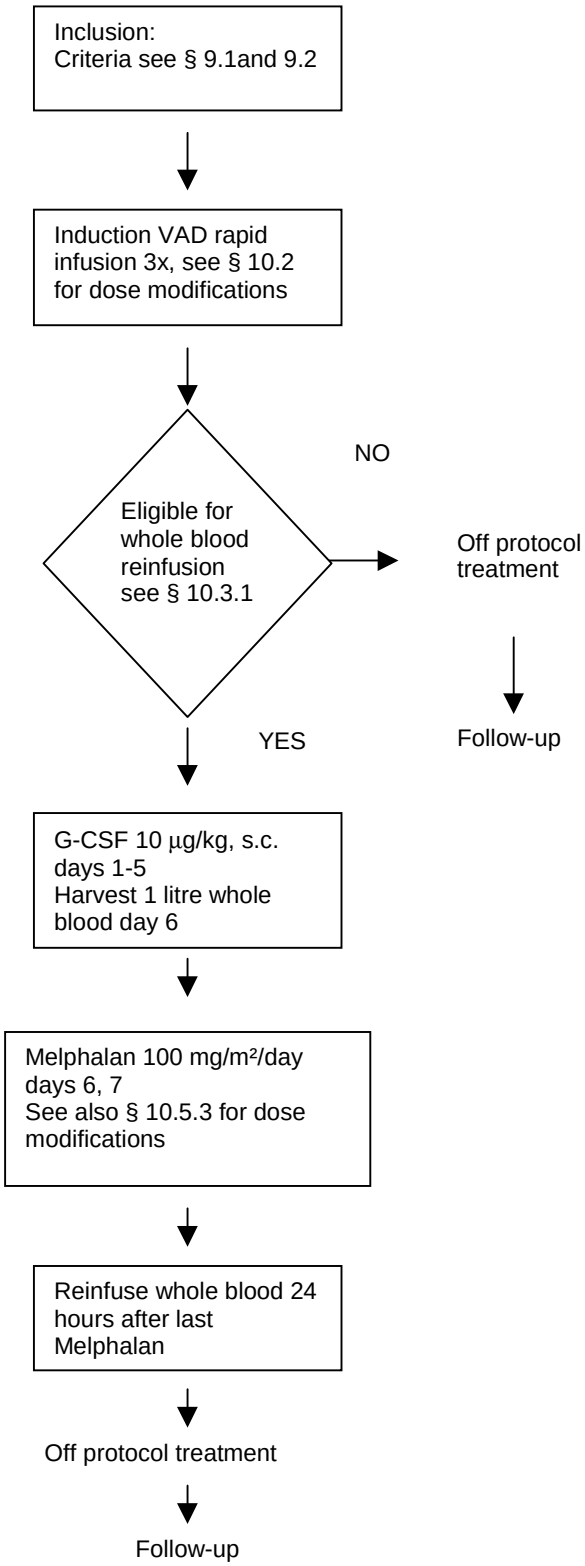
Adjustment : 9 December 2002, not (yet) submitted for approval

1 Scheme of study

1.1 Flow chart PBSCT for AL amyloidosis



1.2 Flow chart Transplantation with unprocessed G-CSF primed whole blood for patient in AZVU



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3 Synopsis

Study phase	Phase II
Study objectives	Evaluation of the effect of intensive treatment
Patient population	Patients with systemic AL amyloidosis, previously untreated or treated with maximal 3 courses of melphalan and prednisone, age < 66 years
Study design	Prospective, multicenter, non-randomized, registration up front
Treatment	Induction with 3 cycles of VAD, then intensification with high dose melphalan followed by PBSCT or whole blood reinfusion
Duration of treatment	Expected duration of 3 cycles of induction treatment inclusive evaluation is about 3 months. For patients eligible for PBSCT/whole blood reinfusion, the additional treatment time is 2-3 months
Number of patients	50-60 patients for induction treatment. Of these patients about one third is expected to receive an autologous transplant
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 2000 End of recruitment : III 2003

4 Investigators and study administrative structure

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		Medical Spectrum Twente, Enschede
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5 Introduction

5.1 AL amyloidosis

The term amyloidosis refers to a family of diverse diseases, all of which are characterised by the deposition of a homogeneous, eosinophilic material in various tissues throughout the body. The major component and diagnostic hallmark of these deposits consists of fibrils with a twisted B-pleated sheet configuration. AL (amyloid light-chain) amyloidosis is an uncommon plasma cell disorder in which depositions of amyloid light chain protein cause progressive organ failure(1). Renal involvement is the most common manifestation of amyloidosis and is the cause of death in 15% of patients. Other clinical features are cardiomyopathy, hepatomegaly, enteropathy and neuropathy. Cardiomyopathy is the most important cause of death (51%). The median survival of systemic AL amyloidosis is only 13 months from diagnosis (2). The diagnosis of amyloidosis is based on a clinical suspicion and established by a tissue biopsy. Usually biopsy of an involved organ will confirm the diagnosis. In systemic amyloidosis, a sample of subcutaneous abdominal fat, obtained by needle aspiration and stained appropriately with Congo red, will be positive in 85% of patients (3); a gingival or rectal biopsy is diagnostic in about 80% of patients (4). The type of amyloid must then be determined. Patients with AL amyloidosis will have a clonal plasma cell dyscrasia. Monoclonal immunoglobulins or light chains are detected in 90% of patients with AL amyloidosis by means of immunofixation electrophoresis of serum or urine. Scintigraphy after injection of patients with 123-I-radiolabeled serum amyloid component (SAP) provides clinically useful information for diagnosis, monitoring of therapy and prognosis in patients with systemic amyloidosis (5).

5.2 Therapy

The goals of therapy in AL amyloidosis include the prevention of further amyloid deposition and the promotion of its resorption. Equally important, are general measures aimed at delaying target organ failure, maintaining quality of life, and prolonging survival while more specific forms of therapy are instituted (6,7,8). lt should be noted that rarely AL amyloidosis presents as a localised disorder, e.g. involving only the laryngeal or bladder region. For these patients no systemic chemotherapy is recommended.

The similarity between multiple myeloma and AL amyloidosis suggested that chemotherapy might constitute useful therapy (3,4). Several randomised prospective clinical trials (9,10) suggested superiority of oral melphalan-prednisone treatment over placebo or colchicine, leading to the establishment of a third randomised study that compared colchicine to melphalan plus prednisone,

and to melphalan plus prednisone plus colchicine (11). The median survival was 8.5 months in the colchicine only group (72 patients), and 17 months in the prednisone melphalan colchicine group (71 patients). In addition, patients who showed a reduction in the serum or urine monoclonal protein at 12 months enjoyed an overall survival of 50 months, compared with 36 months for those without a reduction in the M-component over the same time period (11). Unfortunately, only a small part of patients benefit from low dose cytostatic treatment as response rates to melphalan based regimen varied between
18-30% (8-12). Thus therapy that successfully suppresses the production of the light chain, which is the precursor of amyloid fibrils, appears to improve the survival. However, therapy did not influence the incidence or progression to renal failure of sufficient severity to require dialysis. The loss of renal function probably reflects irreversible damage to the kidney. This is in sharp contrast with proteinuria that can regress and even disappear completely after successful treatment of the underlying plasma cell dyscration. Other similar, randomised studies have confirmed the utility of melphalan based regimens in the therapy of primary amyloidosis (12), especially in patients who do not suffer from significant cardiac or renal impairment.

5.3 Chemotherapy intensification with melphalan

The relatively slow and poor response (which varies between 18-30% in different studies) of patients with systemic AL amyloidosis to oral low dose chemotherapy has prompted interest in dose-intensive regimens. Furthermore, intermediate/high-dose melphalan appears effective therapy in multiple myeloma (13). Similarly, in AL amyloidosis treatment with
high-dose melphalan (200 mg/m²) followed by autologous stem cell support appears to be more effective than standard dose melphalan (14-18). In one study (15) 17 of 25 patients treated with high dose (200 mg/m²) melphalan (68%) were alive after a median follow-up of 24 months (12-38), and the median survival had not been reached. Thirteen of 21 patients (62%) evaluated 3 months post-transplant had complete responses of their clonal plasma cell disorders. Two thirds of the surviving patients (11 of 17) had experienced improvements of amyloid-related organ involvement in all systems, whereas 4 of 17 had stable disease.

5.4 VAD regimen

The combination drug regimen of vincristine, adriamycin (doxorubicin), and dexamethasone (VAD) has been used in patients with AL amyloidosis, yielding an approximate 50% response rate in small series of patients (1,19,20). Recently the clinical response after VAD was further documented in a patient with a nephrotic syndrome due to AL amyloidosis (21). The use of the

VAD regimen instead of melphalan for remission induction has the advantage that the use of stem cell toxic drugs is avoided, thereby not compromising the yield of blood stem cells to be used for subsequent autologous stem cell transplantation.

6 Rationale of the study

This phase II study is to test the feasibility and efficacy of myelo-ablative chemotherapy and autologous stem cell transplantation in patients with AL amyloidosis.
Prior to treatment with high dose melphalan patients with AL amyloidosis will be treated with standard chemotherapy in order to reduce the tumour load prior to hematopoietic stem cell collection. Moreover, a quick reduction of the supply of precursor to the amyloid deposits is mandatory. A shortage of precursor may stop the continuing deposition of amyloid fibrils.
As this is a phase II study, results will be compared with already published results of “low dose” and intensive treatment regimens applied in patients with AL amyloidosis (8-12,15,16,17). Due to the disappointing response rates (18-28%) and short survival (13-18 months) achieved with conventionally dosed melphalan based regimens (8-12) a phase III trial comparing conventional with intensive treatment seems not rational. It can not be excluded that published promising results of intensive treatment in AL amyloidosis are (partly) due to patient selection. For these reasons HOVON has chosen to evaluate prospectively the feasibility and efficacy of intensive treatment in AL amyloidosis. An important feature of the study will be to determine which patient’s groups do or do not
benefit from this approach.

7 Study objectives

1. To determine in a prospective phase II study the efficacy of intensive treatment including peripheral blood stem cell transplantation with regard to clonal response rate, clinical response rate and overall survival.
2. To assess the feasibility of this approach i.e. percentage of patients who will receive an autologous transplantation
3. To assess the value of risk factors at diagnosis, like performance status and organ involvement, for individual patients with AL amyloidosis in relation with dose intensive treatment

8 Study design

The study will be performed as a prospective phase II trial in patients under 66 years. The total number of patients entered will be 50-60.
All patients will be treated with VAD q 4 weeks, 3 courses, followed by melphalan 200 mg/m^2 and PBSCT. See appendix A for grading the WHO performance. Common Toxicity Criteria (see appendix B) are used to evaluate the toxicity of the chemotherapy.
PBSC will be mobilised with G-CSF 10 μg/kg sc for 5 days. In the Department of Hematology, AZVU, G-CSF primed whole blood will be used for rescue after melphalan 200 mg/m^2.

Patients who do not meet the eligibility criteria or who otherwise will not receive melphalan 200 mg/m^2 followed by reinfusion of stem cells of whole blood (AZVU only), will go off protocol treatment but should be followed for survival and for response in case of other treatment modalities. Further treatment of these patients is optional and may consist of melphalan prednisone, dexamethasone or intermediate dose melphalan, 70 mg/m^2 (IDM) and G-CSF.

9 Study population

9.1 Inclusion criteria

- Age under 66 years
- MGUS, multiple myeloma stage I
- Histologically documented systemic AL amyloidosis (see appendix C)
- Untreated or previously treated with maximal 3 courses of melphalan and prednisone
- The patient must give informed consent according to the rules of the hospital.

9.2 Exclusion criteria

- Prior malignancies diagnosed less than 5 years ago, except non-melanoma skin tumours or stage 0 (in situ) cervical carcinoma. Note: *Prior malignancies diagnosed and treated longer than 5 years ago, and in which case it is likely that the patient is cured, are no exclusion criteria.*
- Patients with familial variants of systemic amyloidosis.
- Severe pulmonary, neurologic, psychiatric, cardiac, liver or metabolic disease not related to AL amyloidosis

9.3 Procedure for registration

All patients have to be registered before start of treatment (see §14).

10 Treatments

10.1 Specific care during treatment

Patients with AL amyloidosis have a high risk for treatment related toxicity and death. So specific care should be given during the different treatment phases.

During VAD: Risk for heart failure due to dexamethasone treatment and arrhythmias due to anthracyclines that may bind to amyloid deposits in the myocard.

During cyclophosphamide priming, stem cell collection and stem cell reinfusion: increased risk for fluid overload and arrhythmias.

After melphalan: arrhythmias during febrile episodes.

In general, patients with amyloid cardiomyopathy have a strong increased sensitivity for digoxine and calcium entry inhibitors, thereby increasing the chance of drug toxicity such as cardiac arrest and arrhythmias.

10.2 Induction treatment with VAD

Treatment consists of 3 courses of:

- vincristine	0.4 mg	daily, days 1-4	rapid infusion (15-30 min)
- doxorubicin	9 mg/m^2	daily, days 1-4	rapid infusion (15-30 min)
- dexamethasone	40 mg	daily, days 1-4	p.o.
		days 9-12	p.o. only course 1,3
		days 17-20	p.o. only course 1,3

The second and third course will start at day 29 and day 57 respectively.

10.2.1 Dose modification of VAD

In some categories of patients the VAD regimen should be amended because of risk of enhanced toxicity.

- Vincristine should not be used in patients with more than grade 2 neuropathy (neurosensory, neuromotory) and in patients with signs of autonomic neuropathy
- Dexamethasone only, according to the above schedule, should be given in patients with:

- WHO performance status 4
- severe cardiac disease including one or more of the following signs:
  * NYHA grade 4 heart failure (see appendix D)
  * cardiac ejection fraction < 45%
  * mean left ventricular wall thickness on echocardiogram > 15 mm
  * syncope caused by dysrythmia or severe conduction defect (not treatable with a pacemaker)
- inadequate liver function which is likely to be related to AL amyloidosis, i.e. bilirubin 2.5 times the upper normal value

10.2.2 Supportive care during VAD and modified VAD

- ♦ pneumococcen prophylaxis with cotrimoxazol 2x 480 mg daily is recommended or otherwise according to local protocols
- ♦ prophylaxis of infections in case of severe neutropenia (ANC < $0.5x10^9$/l) according to local protocols
- ♦ fluconazole 50 mg every 24 hours or according to local protocols
- ♦ antacid

10.3 Intensification after induction therapy

In all participating hospitals except the AZVU, Amsterdam, PBSCT will be performed in eligible patients (see § 10.3.1) after melphalan 200 mg/m² as described in § 10.4.2. PBSC for support will be obtained 2-6 weeks prior to transplantation after priming with G-CSF alone or combined with cyclophosphamide as described in § 10.4.1 and flow chart on page 2. In the department of Haematology, AZVU Amsterdam, eligible patients (see § 10.3.1) will be treated with melphalan 200 mg/m² followed by whole blood rescue as described in § 10.5.2 and flow chart page 3. Unprocessed whole blood will be collected after priming with G-CSF alone for 5 days preceding melphalan 200 mg/m².

10.3.1 Inclusion criteria for stem cell collection and PBSCT/whole blood reinfusion

Patients have to meet the following criteria before stem cell collection/PBSCT, otherwise they go off-protocol treatment.

- ♦ WHO performance status 0-2

- NYHA 1-3
- cardiac ejection fraction ≥ 45%
- no active infections
- absence of severe pulmonary, neurologic, psychiatric disease.
- bilirubin and transaminases of less than 2.5 times the upper limit of normal values.
- WBC ≥ 2 x 10^9/l, platelets > 100 x 10^9/l

10.4 Melphalan 200 mg/m² followed by peripheral blood stem cell transplantation (all hospitals except AZVU, Amsterdam)

10.4.1 Stem cell mobilisation scheme

Stem cell collection will be initiated 4-6 weeks after start of the third course of VAD or modified VAD.
Stem cells will be preferentially mobilised using G-CSF at a dose of 10 μg/kg. The use of G-CSF alone has the advantage of avoiding the necessity of hyperhydration with its associated risks in renally or cardially compromised patients with AL amyloidosis. The collection of PBSC after priming with cyclophosphamide 4 g/m² and G-CSF however is allowed.

G-CSF s.c. 10μg/kg (divided in 2 doses) will be administered for 5 days. Stem cell collection will be performed on day 4 and 5 (or longer). At least 2.5 x 10^6 $CD34^+$/kg are required for transplantation. In case insufficient stem cells are collected the procedure may be repeated (possibly after the use of cyclophosphamide priming) or alternatively bone marrow stem cell collection may be performed.

10.4.2 Melphalan 200 mg/m² followed by PBSCT

This phase will start between 2-6 weeks after stem cell collection.
Melphalan 100 mg/m²/day will be given as rapid infusion on day -3,-2. 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 if necessary.

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.

10.4.3 Melphalan 100 mg/m² in patients with renal insufficiency

Although melphalan pharmacokinetics is not adversely affected by impaired renal function, general toxicity of melphalan 200 mg/m² in patients with a creatinine clearance ≤ 40 ml/min may be increased (22).
For patients with a creatinine clearance ≤ 40 ml/min, melphalan 100 mg/m² will be administered on day -2 only.

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

- implacement of central venous catheter
- menstruating premenopausal females will be started on anovulatory drugs
- antibacterial and antifungal prophylaxis should be given according to local protocols
- antistreptococcus prophylaxis is recommended from day +4 till day +14.

10.5 Melphalan 200 mg/m² followed by unprocessed G-CSF-primed whole blood (only AZVU, Amsterdam)

10.5.1 Collection of unprocessed whole blood

This phase will start between 4-6 weeks after start of the third course of VAD or modified VAD. G-CSF s.c., 10 μg/kg will be administered in one gift, at 16.00 hours from day 1 through day 5. At day 6, 2 CPDA containing blood collection bags will be filled, each with 500 ml blood. In between, 500 ml NaCl 0.65% will be infused. The two whole blood bags will be stored at 4°C, in a blood bank refrigerator (23,24).

10.5.2 Melphalan 200 mg/m² followed by whole blood rescue

Melphalan 100 mg/m²/day will be given as rapid infusion on day 6 and 7. 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 if necessary.

Exactly 24 hours after the second melphalan dose, the two whole blood bags will be reinfused, each in 2 hours. Total time of storage should not exceed 72 hours.

10.5.3 Melphalan 100 mg/m² in patients with renal insufficiency

Although melphalan pharmacokinetics is not adversely affected by impaired renal function, general toxicity of melphalan 200 mg/m² in patients with a creatinine clearance ≤ 40 ml/min may be increased (25).
For patients with a creatinine clearance ≤ 40 ml/min, melphalan 100 mg/m² only will be administered on day 6.

10.5.4 Supportive care during melphalan 200 mg/m² (100 mg/m²) aplasia

- implacement of central venous catheter
- menstruating premenopausal females will be started on anovulatory drugs
- antibacterial and antifungal prophylaxis should be given according to local protocols
- antistreptococcus prophylaxis is recommended from day +4 till day +14 after whole blood infusion.

11 End of protocol treatment

Reasons for going off protocol treatment are:

1. Completion of protocol treatment
2. Not eligible for mobilisation after VAD or modified VAD
3. Death
4. Refusal of the patient to continue therapy and/or further evaluations

12 Required clinical evaluation

12.1 At entry (See appendix F)

Aim of the clinical evaluation at entry is to know which organs are involved and the severity of the involvement: **See appendix E for the definitions of organ involvement**.

12.1.1 Medical history

Standard medical history plus special attention for:

- Autonomic neuropathy
- Syncope

- Bleeding tendency
- Obstipation/diarrhoea
- Carpal tunnel syndrome
- Polyneuropathy
- Family history
- Performance

12.1.2 Physical examination

Standard physical examination plus special attention for:

- Macroglossia
- Hepatosplenomegaly
- Orthostatic hypotension
- Carpal tunnel syndrome
- Polyneuropathy
- Shoulder pads
- Oedema

12.1.3 Laboratory investigations

Routine blood evaluation including

- Haemogram, creatinine, BUN, bilirubin, alk. fosfatase, liver enzymes, total proteins plus spectrum, including albumen, CRP
- Qualitative and quantitative M-protein
- Qualitative and quantitative urine M-protein/24h
- Quantitative total urine proteins/24h
- Serum β_2–microglobulin
- Creatinine clearance (clinical indication)
- Bone marrow biopsy

  Bone marrow aspirate in heparin/MEM:

  - morphology
  - immunophenotyping of cytoplasmic, surface immunoglobulin expression
  - DNA analysis (VDJ sequencing) (facultatory)

12.1.4 Specific investigations

- ECG
- X thorax
- Echocardiography with measurement of ventricle wall thickness
- Cardiac ejection fraction by scintigraphy

12.1.5 Additional investigations on clinical indication

- Echography abdomen
- Spirometry
- Survey for autonomic neuropathy
- Resorption tests (xylose, vitamin A curve, Schilling test)
- Swallow scintigraphy
- Stomach passage scan
- Fasting cortisol, ACTH test
- EMG

12.2 During treatment and follow-up (see flow chart appendix F)

- Medical history and physical examination.
  - After last VAD, after PBSCT: at +3, +6, +9, +12 months. Thereafter every 6 months
- Routine laboratory including serum M-protein/urine M-protein measurement:
  - After last VAD, after PBSCT: at +3, +6, +9, +12 months. Thereafter every 6 months
- Bone marrow biopsy, evaluation of involved organs:
  - After last VAD, after PBSCT: at +3, +12 months, thereafter once a year until + 60 months, at + 120 months and at clinical or clonal relapse or progression
- ECG and performance:
  - After last VAD, after PBSCT: at +3, +6, +9, +12 months. Thereafter every year.
- Cardiac ejection and cardiac echo
  - After last VAD. Thereafter on indication only, especially in patients with cardiac involvements

Patients who did not receive PBSC are followed as well: routine laboratory every 3-6 months; bone marrow biopsy and evaluation of involved organs 3 months after last (modified) VAD. Thereafter once a year.

12.3 Justification of diagnostic procedures

All diagnostic procedures are part of a normal screening and follow-up program which should be applied to patients who are treated for AL amyloidosis.

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)
- hospitalisation or prolongation of hospitalisation
- 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 patients 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 patients 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 implicity 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 Registration

The patient should be registered immediately after diagnosis 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 Proces; 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:

- Protocol number
- Institution's name
- Name of physician in charge
- Patient's name code
- Date of birth
- Sex
- Hospital record number (optional)
- Inclusion and exclusion criteria
- Date of start treatment

At the time of registration each patient will be given a unique sequential identification number.

15 Forms and procedures for collecting data

15.1 CRF's and schedule for completion

LIST OF FORMS

Form nr	Title
1	Registration form
2	On study form
3A	Evaluation form – on study -
3B	Evaluation form – treatment -
3C	Evaluation form – follow up -
4	VAD treatment
5	Treatment response form
6	Intensification eligibility form
7	Stem cell mobilization-/whole blood-collection form
8	Melphalan treatment and PBSCT/whole blood reinfusion form
9	Off treatment form
10	Follow up form
11	Side effects form
12	Infection report form
13	General comments form

Table for filling out forms

	Forms														
	1	2	3A	3B	3C	4	5	6	7	8	9	10	11	12	13
Registration	**X**														
On study		**X**	**X**												**(X)**
VAD treatment				**X**		**X**	**X**	**X**					**(X)**	**(X)**	**(X)**
Stem cell/whole blood collection									**X**				**(X)**	**(X)**	**(X)**
Melphalan & PBSCT/ whole blood reinfusion				**X**			**X**			**X**			**(X)**	**(X)**	**(X)**
End of treatment											**X**	**X**			**(X)**
Follow up					**X**							**X**			**(X)**

(x) fill out if necessary, see instructions

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

16 Statistical considerations

16.1 Sample size

The yearly incidence of AL amyloidosis is about 8 per million persons (25). As fifty percent of the patients are ≤ 65 years about 60 patients/year are potentially candidate for the study. It is estimated that 20 patients per year will be requested of whom maybe one third will ultimately receive an autologous transplant. The aim is to enter a total of 50-60 patients in the study in 3 years time. The main endpoints will be response (clonal and clinical), the percentage of patients that will ultimately receive an autologous transplant and overall survival.

16.2 Interim analyses and early stopping rules

As this study examines the feasibility of myelo-ablative chemotherapy and autologous stem cell transplantation in patients with AL amyloidosis, the percentage of patients that is ultimately transplanted is considered to be the most relevant endpoint for early discontinuation of the study. It

is expected that about one third of the patients will receive an autologous transplant. Should this be less than 20%, the study should be considered for early discontinuation.

A multiple-stage procedure (J.R. Schultz et al. Multiple-stage procedures for drug screening, Biometrics, Volume 29, 293-300. 1973) is used with two interim analyses after 20 and 40 evaluable patients with the possibility of early discontinuation. The stopping rules are determined in such a way that the probability of early stopping is small if the true percentage of transplanted patients is 35% or more, while the probability is considerable that the trial will be stopped early if the true percentage of transplanted patients is 20% or less.
Using a false-positive error rate (false positive result for an ineffective treatment) $\alpha = 0.05$ and also a false negative error rate $\beta = 0.10$, the following three-stage design appears:

1. If of the first 20 evaluable patients only 3 or less have been transplanted, discontinue the trial, otherwise go on;
2. The second interim analysis will be performed after 40 evaluable patients: if only 8 or less patients have been transplanted, stop the trial, otherwise continue until 60 patients.

Probability of early stopping		
	True proportion of transplanted patients	
Evaluable patients	0.20	0.35
20	41%	4%
40	24%	2%

The table shows that if the true percentage of transplanted patients would be 20%, there would be a probability of 41% to discontinue the trial after 20 evaluable, while the probability of (undeserved) early discontinuation would be only 4% if the true percentage of transplanted patients is 35%.

3. The final analysis will be based on 60 evaluable patients: when 16 or less patients have been transplanted, this treatment will be rejected. In case 17 or more transplants have been performed, the transplanted patients should be evaluated in more detail (e.g. for unacceptable high transplant related mortality) to see whether the results look promising and merit further testing, e.g. in a randomised trial.

17 Criteria of evaluation and endpoints

Response will be determined by evaluating clonal cell population (clonal response) and clinical symptoms (clinical response).

17.1 Clonal response

In many cases of primary AL amyloidosis the abnormal clonal cell population can not be quantified, as there are only trace amounts of monoclonal proteins present in serum and or urine (< 1 g M-protein) and very few monoclonal plasma cells present in the bone marrow. Therefore partial response can only be defined when the M-protein at diagnosis in serum and/or urine is more than 5 g/l or 100 mg/24h respectively.

Complete clonal response: Complete disappearance of monoclonal proteins (as determined by immunofixation) from serum and in 10x concentrated urine and normalisation of the number of plasma cells (< 5%) and kappa-lambda ratio between 1 and 4 as determined by immunophenotyping of the bone marrow aspirate.

Partial clonal response: Greater than 50% reduction in serum and 24h urine monoclonal proteins in patients with a light chain excretion of 100 mg or more in the 24h urine (without being explained by diminished protein excretion caused by progressive renal failure). However, the latter may be difficult to assess and should be measured at least on two separate days.

Clonal relapse: Detection of pretherapy M-protein (serum or urine) or the reversion to the prior κ or λ clonal dominance in bone marrow aspirates after complete clonal response.

clonal progression: In patients with or without a partial response doubling of M-protein in serum to more than 5 g/l or a doubling of the light chains in urine above at least 200 mg/24h. However, the latter may be difficult to assess and should be measured at least on two separate days.

Clonal persistence: No response nor progression.

17.2 Clinical responses

Improvement

a. Renal involvement: a 50 percent decrease in the 24-hour protein excretion, in the absence of progressive renal insufficiency, in patients presenting with proteinuria (urinary protein, >0.5 g per 24 hours).

b. Cardiac involvement: a decrease of ≥ 2 mm in mean left ventricular wall thickness in patients with baseline wall thickness > 11 mm, a decrease in two classes in NYHA class (i.e., from 3 to 1), or an increase of 20 percent in the ejection fraction.

c. Hepatic involvement: a reduction in the size of the enlarged liver span by at least 2 cm and a 50 percent decrease in serum alkaline phosphatase.

d. Neuropathic (peripheral and autonomic) involvement: improvement based on clinical evaluation, appropriate non-invasive tests, or EMG

e. Serum albumin: an increase of at least 10 g/l in serum albumin, given an initial value of less than 30 g per litre and stable renal function.

f. Other involvement: improvement according to the treating physician in other amyloid related symptoms.

Stabilisation (kidney, heart, liver, nerves, serum albumin) is defined as no improvement and no progression

Progression

a. Renal involvement: an increase of more than 2.5 gram in the 24-hour protein excretion (two different measurements) or a decrease in the endogenous creatinine clearance of more than 30 ml/min (two different measurements).

b. Cardiac involvement: worsening of clinical signs or symptoms, worsening of two classes in the NYHA class (i.e., from 1 to 3), an increase of 2 mm in mean left ventricular wall thickness in a patient with a baseline wall thickness ≤ 11 mm, or a decrease of 20 percent in the ejection fraction

c. Hepatic involvement: an increase of liver span with at least 2 cm, or a 50 percent increase in serum alkaline phosphatase (at least above 200 U/l).

d. Neuropathic (peripheral and autonomic) involvement based on clinical evaluation appropriate non-invasive tests, or EMG

e. Serum albumin: a decrease of at least 10 g/l in serum albumin.

f. Other involvement: progression according to the treating physician in other amyloid related symptoms.

Clinical improvement is present when one or more of the improvement criteria (see above) are present without any criterion of progression (see above).
Clinical stabilisation is present when no criteria of improvement or progression are present.
Clinical progression is present when one or more criteria of progression are present regardless of any other criterion of improvement. However, other causes of progression of organ dysfunction, especially drug-related causes, should be excluded or at least made unlikely.
Clinical relapse is progression after and compared to a preceding clinical improvement

17.3 Overall survival

Time from registration until death. Patients still alive or lost to follow-up are censored at the last day they were known to be alive.

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 (South Africa Amendment 1996) and the ICH-GCP Guidelines of 17 January 1997.

18.3 Patient information and consent

Written Informed Consent of patients is required before registration. The procedure and the risks and the opinions for treatment in AL amyloidosis 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/randomised 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 Centre, 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 randomised 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 registered/randomised in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomised 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)

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AL	Amyloid Light-chain
ALAT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
ASAT	Aspartate Animo Transferase
BM	Bone Marrow
BMT	Bone Marrow Transplant
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
CTS	Carpal Tunnel Syndrome
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMG	Electromyogram
FISH	Fluoro In Situ Hibridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastroa-intestinal
HOVON	Dutch/Belgian Hematology-Oncology Cooperative Group
ICH	Internation Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IDM	Intermediate Dose Melphalan
IRB	Institutional Review Board
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PO	Per Os
SAE	Serious Adverse Event
SAP	Serum Amyloid P component
SCT	Stem Cell Transplantation
TOP	Trial Online Process
VAD	Vincristine, Adriamycin (doxorubicin), Dexamethasone
WBC	White Blood Count
WHO	World Health Organisation

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A. 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

B. Common toxicity Criteria

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

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

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

C. The diagnosis of systemic AL amyloidosis

In most cases systemic AL amyloidosis can be diagnosed without any problem. However, because of prognostic and therapeutic consequences, the diagnosis should be indisputable and firmly based on three elements:

1. A histological proof of amyloid in a biopsy specimen
2. The systemic nature of the amyloidosis should be established
3. The amyloidosis should be characterised as the AL type

Comments:

1. A biopsy specimen with amyloid should be positively stained with Congo red dye, showing apple-green birefringence in polarised light. If there is any doubt, another specimen should be stained or an experienced pathologist should review the original biopsy specimen.
2. The systemic nature of the amyloidosis can be established in different ways:
   a. Some sites of the body (such as eyelid, cornea, thyroid, parathyroid glands, pituitary gland, skin, cardiac atria, aorta, lung, pleura, trachea-bronchial tree, larynx, pharynx, ureter, bladder, urethra, pancreas, prostate, seminal vesicles, joints, ligaments, bone marrow, cerebrum, and large amyloid tumours) are sites where localised amyloid can be found. In these cases amyloid must be detected somewhere else in the body to exclude localised amyloidosis.
   b. Some sites are exclusively involved in systemic amyloidosis, such as kidneys, liver, nerves, and spleen. If such a site is positive for amyloid (by histology or scintigraphy with SAP) systemic involvement may be assumed.
   c. All other sites (such as bone marrow, subcutaneous fat, heart, bowel, lung, joint, etc.) are often involved in systemic amyloidosis. In this case it is recommended to show amyloid to be present in two different organs or tissues. It is however sufficient to have histological proof at one site (such as bone marrow, skin, subcutaneous fat, or rectum) and clinical involvement (such as nephrotic syndrome, hepatomegaly, macroglossia, or cardiomyopathy) at the other site.
3. Amyloidosis should be characterised as AL type by the following guidelines (6):
   a. An underlying monoclonal plasma cell dyscrasia is a prerequisite for the diagnosis

and has to be present (sometimes hard to detect) in serum, urine, or bone marrow.

b. When a chronic inflammatory disease is present or in case amyloid is clinically restricted to the kidneys or gastrointestinal tract, it is recommended to exclude AA amyloidosis by immunohistology or immunohistochemistry.
c. When a family history for amyloidosis is present or in case amyloid is clinically restricted to heart, nerves, or eyes, it is recommended to exclude ATTR amyloidosis by immunohistology and by screening of the serum for variants of transthyretin (26). If necessary the transthyretin gene can be analysed to exclude a mutation.

D. NYHA* classification of heart failure

Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest

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

E. Organ involvement

Organ (and tissue) involvement in AL amyloidosis (based on ref. 2, 11, and 12 with some modifications):

The predominant organ involvement is determined based on clinical consensus (often the way of presentation or the most prominent signs and symptoms)

- Renal
- Cardiac
- Hepatic
- Peripheral neuropathy
- Other

* Renal involvement is defined as proteinuria >0.5 g/24h, or the serum creatinine more than 106 μmol/l (or an endogenous creatinine clearance below 90 ml/min).

* Cardiac involvement is defined as the presence of a mean left ventricular wall thickness on echocardiogram >11 mm in the absence of a history of hypertension or valvular heart disease, or as the presence of unexplained low voltage (<0.5 mV) on the electrocardiogram.
Clinical status is based on history, physical examination, and New York Heart Association (NYHA) heart failure class (see Appendix D). Patients who are NYHA class 1 with evidence of cardiac amyloid by echocardiogram or electrocardiogram are categorised as having asymptomatic cardiac involvement. Patients who are NYHA class 2 or higher with evidence of cardiac involvement are categorised as having predominant cardiac involvement (amyloid cardiomyopathy).

* Hepatic involvement is defined as a hepatomegaly (liver span > 15 cm) and an alkaline phosphatase >200 U/l.

* Peripheral polyneuropathy is defined as the typical complaints of sensory or motor neuropathy and confirmed by a neurologist

* Autonomic neuropathy is defined as the presence of orthostatic hypotension (a drop in systolic blood pressure of ≥ 20 mm Hg and a drop in diastolic blood pressure ≥ 10 mm Hg and a rise in heart rate of ≤ 10 beats per minute during the first three minutes after a change from the supine to the upright posture) or

abnormal autonomic testing by the method of Ewing and Clark (score > 5 points) not caused by medication (27)

* Splenic involvement is defined as a splenomegaly (palpable spleen with echographic length more than 13 cm) or “several” Howell-Jolly bodies in the differential leukocyte count (more than 3 per glass slide) (28)
* Glossomegaly is defined as an acquired enlargement of the tongue, often with indentations and stiffness
* Carpal tunnel syndrome (CTS) is defined by history (pain at night and the early morning, paresthesia in the finger tips) with positive sign of Tinel or confirmed by elektro-myogram (EMG)
* Arthropathy is defined as the typical clinical picture of shoulder pads with or without the non-inflammatory involvement of wrists and finger joints
* Gastrointestinal involvement is defined as diarrhoea (loose stool more than three times a day for more than four weeks without a known cause) or constipation both of recent onset without the presence of autonomic neuropathy or defined as weight loss (more than 10% of body weight) and malabsorption confirmed by absorption tests (such as xylose or vitamin A absorption)
* Pulmonary involvement is defined by radiography as an interstitial (reticular or diffuse) pattern or a pleural effusion without prominent cardiac involvement (29)
* Thyroid involvement is defined as hypothyroidism or goitre not caused by another disease
* Adrenal involvement is defined as (sub)clinical adrenal insufficiency, with a decreased morning cortisol level and confirmed by an ACTH stimulation test
* Miscellaneous:
    - Skin lesions such as petechiae, ecchymoses, papules, plaques, nodules, tumours, bullous lesions, alopecia, dystrophy of the nails
    - Muscular involvement such as dystrophy and pseudohypertrophy
    - Temporal artery involvement
    - Myocardial ischemia and non-specific precordial pain
    - Reduced taste perception
    - Sicca syndrome
    - Gastrointestinal manifestations such as pseudo-obstruction, tumours, ulceration, bleeding, and perforation
    - Bleeding and thrombosis

F. Flowsheet onderzoek Amyloidose patiënten

	inclusie	na laatste VAD	3 mnd na Melphalan + PSCT	6 mnd na Melphalan + PSCT	9 mnd na Melphalan + PSCT	12 mnd na Melphalan + PSCT + jaarlijks
Datum						
Anamnese	X	X	X	X	X	X
Lichamelijk onderzoek	X	X	X	X	X	X
Performance status	X	X	X	X	X	X
BM morfologie + immuuntypering (cytoplasmatische opp Ig expressie) + invriezen van viabele cellen voor DNA analyse (+evt. FISH)	X	X	X			X
Crista biopsie	X	X	X			X
Routine lab. onderzoek, waaronder haemogram, kreat, ureum, bili, AF, ASAT, ALAT, γGT, TE + spectrum, albumine, CRP,β_2-microglobuline	X	X	X	X	X	X
Kwantitatief serum M proteïne	X	X	X	X	X	X
24 uurs urine op kwantitatief Bence Jones en totaal eiwit en kreatinine	X	X	X	X	X	X
Kreatinine klaring	#	#	#	#	#	#
ECG	X	X	X	X	X	X
X thorax	X	X	#	#	#	#
Echocardiogram met meting van ventrikelwanddikte	X	*	*			*
Cardiale ejectiefractie (scintigrafisch)	X	X	*			*
<u>Op indicatie</u> Echo abdomen	#	*	*			*
Spirometrie	#	*	*			*
Onderzoek m.b.t. autonome neuropathie	#	*	*			*
Slikscintigrafie	#	*	*			*
Maagontledingsonderzoek	#	*	*			*
Nuchter cortisol, ACTH stimulatie test	#	*	*			*
EMG	#	*	*			*
24 uurs Holter	#	*	*			*
Overig onderzoek	#	*	*			*
SAP scintigrafie	**		**			1, 2, 5, 10 years

#: op indicatie, *: herhalen wanneer initieel afwijkend of op indicatie, **: geïndiceerd bij patiënten die in staat zijn tot deze extra belasting (= drie dagen naar Groningen, namelijk van woensdag ca. 10.30 u tot vrijdag ca. 12.00 u). Onderzoek vindt plaats in AZG, Groningen, plannen na informed consent (zie aparte informatie-folder) en in overleg met Dr. Hazenberg, reumatoloog AZG.

G. Patiënteninformatie

PATIENTENINFORMATIE VOOR DE BEHANDELING VAN PATIENTEN MET AMYLOIDOSE

Inleiding

Bij u is de diagnose amyloidose gesteld en u bent gevraagd deel te nemen aan een studie waarin de waarde van behandeling met intensieve chemotherapie (=anti-kanker medicijnen) wordt onderzocht. Dit onderzoek wordt namens HOVON (Stichting Hemato-Oncologie voor Volwassenen Nederland) uitgevoerd in een groot aantal Nederlandse en Belgische ziekenhuizen.

Wat is amyloidose: De aandoening wordt veroorzaakt door een woekering van abnormale cellen (plasma cellen) in het beenmerg die een abnormaal eiwit, het zgn. amyloid, produceren. De ziekteverschijnselen ontstaan doordat dit amyloid kan neerslaan in verschillende organen (hart, lever, nieren, zenuwweefsel, maag en darmen) waardoor de functie van die organen in meer of mindere mate verstoord wordt. Slaat het amyloid neer in de nieren dan treedt vaak ernstig eiwitverlies met de urine op met als gevolg oedeem. Slaat het amyloid neer in het hart dan kan de hartfunctie ernstig verstoord raken met als gevolg benauwdheidsklachten. De symptomen waarmee de ziekte zich presenteert kan sterk variëren afhankelijk van welk orgaan (het meest) is aangedaan.

De huidige behandeling; de standaard behandeling voor amyloidose bestaat uit een combinatie van het anti-kankermedicijn melphalan met prednisone. Beide medicijnen worden 1x per 4-6 weken gedurende 4 dagen in tabletvorm ingenomen. De voordelen van deze therapie zijn een goede verdraagzaamheid (weinig misselijkheid en braken), géén haaruitval en poliklinische behandeling. Poliklinische controle 1x per 3-4 weken is vaak voldoende. De nadelen van deze behandeling zijn het lage percentage patiënten (20-30%) dat goed reageert en de korte duur van aanhouden van een eventuele goede reactie. Ook bij patiënten die verbeteren komen de verschijnselen vaak binnen enkele maanden weer terug en een adequate behandeling is dan in het algemeen niet meer mogelijk.

De intensieve behandeling: In de laatste jaren is onderzocht of een zwaardere behandeling met chemotherapie met stamceltransplantatie (intensieve chemotherapie) de vooruitzichten van de patiënt met de amyloidose kan verbeteren. Er zijn aanwijzingen dat een groter

percentage patiënten positief op de behandeling reageert en dat bij hen die goed reageren de ziekte langdurig onder controle kan komen. De ervaring met intensieve behandeling bij amyloidose is echter beperkt, waardoor het niet zeker is dat deze behandeling uiteindelijk beter is dan de standaard therapie. Een andere factor die van belang is dat de intensieve behandeling met meer bijwerkingen gepaard gaat en ook voor een deel in het ziekenhuis moet plaats vinden (zie onder).

Doel van het onderzoek: het doel van het onderzoek is om

1. vast te stellen hoeveel patiënten positief (verbetering van klachten en verbetering van het beenmerg) op intensieve behandeling reageren en hoe lang een eventuele goede reactie aanhoudt
2. te bepalen wat de bijwerkingen van deze behandeling zijn en
3. vast te stellen bij welke patiënten intensieve behandeling *wel* en bij welke patiënten intensieve behandeling *niet* goed werkt, zodat later bij diagnose al kan worden vastgesteld wie van deze nieuwe benadering eventueel het meest baat heeft.

De uiteindelijk uitkomsten van deze studie zullen vergeleken worden met de resultaten die zijn bereikt na behandeling met de standaard behandeling.

De intensieve behandeling:

Na uitgebreid onderzoek vooraf (zie onder voorbereidende onderzoeken) volgt de behandeling die in 3 fasen plaats vindt. In de eerste fase wordt poliklinische chemotherapie volgens het VAD schema gegeven. Hiervoor is gekozen vanwege de goede ervaring met deze kuren bij behandeling van het verwante ziektebeeld multipel myeloom. In de tweede fase worden uit uw bloed de beenmergstamcellen geoogst en ingevroren (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. Hiervoor wordt u enkele weken in het ziekenhuis opgenomen.

Onderzoek voorafgaand aan de behandeling.

U hebt al een aantal onderzoeken, zoals een beenmergpunctie achter de rug omdat bij u de diagnose amyloidose al is gesteld. Het aanvullende onderzoek is erop gericht om na te gaan in welke organen het amyloid is neergeslagen en in hoeverre er geen belemmeringen bij u aanwezig zijn de behandeling uit te voeren. Naast routine bloed en urine onderzoek zal in ieder geval hartfunctie onderzoek plaats vinden. Middels een zogenaamde echografie en met nucleair onderzoek zal gekeken worden naar de dikte van de hartspier en de

pompfunctie. Deze kan namelijk gestoord zijn bij amyloidose. De behandeling is alleen veilig uit te voeren als de hartfunctie redelijk goed is. Als blijkt dat de hartfunctie niet goed genoeg is wordt de eerst fase van de behandeling aangepast (zie onder: aangepaste VAD kuur).

Eerste fase: 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 prednisone. Dit middel wordt in tabletvorm gegeven gedurende 4 dagen. 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. Vincristine kan tintelingen in vingers of voeten veroorzaken. Indien dit het geval is, dient u dit aan de arts te melden. De VAD kuur wordt meestal poliklinisch gegeven gedurende 3 maanden 1 maal per maand.

Aangepaste VAD-kuren

De VAD kuur zal worden aangepast indien er bij u hartafwijkingen zijn vastgesteld, die een verhoogd risico op bijwerkingen van de vincristine en adriamycine geven. In dit geval wordt alleen dexamethason toegediend.
Ook bij ernstig gestoorde zenuwgeleiding (polyneuropathie), hetgeen zich kan uiten in tintelingen in armen of benen, zal de VAD kuur worden aangepast. In dit geval wordt alleen adriamycine en dexamethason gegeven.

Onderzoek na afloop van de eerste fase van de behandeling met VAD.

Naast routine bloed en urine onderzoek zal ook een beenmergpunctie verricht worden om het effect op het abnormale plasma cellen te beoordelen. Ook zal het hartfunctie onderzoek herhaald worden. **Als de hartfunctie teveel verminderd is (of was en onvoldoende verbeterd) en/of er bij de andere onderzoeken (te) ernstige afwijkingen geconstateerd zijn, is aanvullende intensieve behandeling niet verantwoord.** Uw behandelend arts zal dan met u overleggen over alternatieve vormen van therapie zoals “milde “ chemotherapie. Zijn er geen bezwaren gevonden dan volgt de fase van stamcel verzameling, 4 tot 6 weken na de derde VAD kuur.

Stamcelverzameling

Vier tot zes weken na de derde VAD kuur zult u gedurende 4 tot 5 dagen met een beenmergstimulerende factor worden behandeld: 'G-CSF'. Dit middel stimuleert de

aanmaak van beenmerg stamcellen. Na een aantal dagen verschijnen deze stamcellen in het bloed en kunnen dan hieruit “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 dat geheel verdwijnt na het staken van het gebruik van het medicament.
Op het moment dat er stamcellen in het bloed verschijnen, meestal dus de 4de dag na het begin van de 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 'stamcelferese' 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 een transplantatie moet de stamcelferese soms de volgende dag herhaald worden. De geoogste bloedstamcellen worden ingevroren totdat ze moeten worden toegediend.

De intensieve behandeling met autologe stamceltransplantatie

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. *Hoge Dosis Melfalan* therapie. Het doel is om met deze hoge dosis chemotherapie zoveel mogelijk (resterende) kwaadaardige plasma cellen uit te schakelen zodat verdere amyloid neerslagen in het lichaam voorkomen wordt en de orgaan functies kunnen herstellen. Omdat door de intensieve behandeling ook het normale beenmerg volledig uitgeschakeld wordt, moet deze behandeling ondersteund worden door een stamceltransplantatie. Hiervoor worden de stamcellen 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 de gehele opname blijft zitten, kunnen infusen gegeven worden en kan bloed worden afgenomen voor onderzoek. Daarna kan de intensieve behandeling beginnen. De chemotherapie (Melphalan) 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 melphalan) 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.

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 beenmergpunctie 1x per jaar. De andere onderzoeken zijn afhankelijk van welke organen door de amyloidose aangedaan waren. Was dit het hart, dan zullen regelmatig (2x per jaar) hartfunctie onderzoek plaats vinden. Was de lever vergroot, dan zullen er regelmatig foto's (echo) van de buik gemaakt worden enz.

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 hartfunctie onderzoek. Dit gebeurt zowel bij diagnose en tijdens het verloop van de behandeling. In essentie zijn er geen extra onderzoeken verbonden aan de intensieve behandeling. De extra belasting komt door de behandeling zelf. Zoals u hierboven kunt lezen wordt de standaard behandeling geheel poliklinisch uitgevoerd en zijn de bijwerkingen van de behandeling gering. De bijwerkingen van de verschillende fasen van de intensieve behandeling zijn groter en bovendien vindt een deel van de therapie (de stamcel transplantatie) in het ziekenhuis plaats. Hoewel autologe stamceltransplantatie inmiddels een routine procedure is geworden en al bij duizenden patiënten met verschillende kwaadaardige aandoeningen is uitgevoerd kunnen er toch fatale complicaties optreden door de transplantatie zoals onbehandelbare infecties, bloedingen, long- en leverstoornissen. De ervaring met autologe stamceltransplantatie bij amyloidose is beperkt. De ervaring tot nog toe laat zien dat vaak

door de mindere conditie (aantasting organen door het amyloid) de sterfte door de behandeling rond de 10% ligt.

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 ondergetekende of met de andere artsen van de afdeling Bloedziekten.

Privacy

Uw persoonlijke gegevens zullen worden behandeld volgens alle wettelijke regelingen met betrekking tot vertrouwelijkheid. Uw gegevens worden opgeslagen in en geanalyseerd door een computer. Tijdens deze analyses zal het niet mogelijk zijn de gegevens tot u te herleiden. Uw naam zal in geen enkel studierapport voorkomen.

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.

Weigering/terugtrekking

Het staat u geheel vrij om aan dit onderzoek mee te doen of deelname te weigeren. Bovendien kunt u zich op ieder door u gewenst moment uit dit klinisch onderzoek terugtrekken, zonder nadere verklaring van uw kant. Uw weigering of terugtrekking heeft geen enkele nadelige consequentie voor de kwaliteit van de behandeling die u nodig heeft. Wij vragen u wel de voorschriften van uw behandelend arts te volgen en geen behandelingen te ondergaan die u niet met uw arts heeft besproken. U zult zoveel mogelijk volgens het onderzoeksprotocol worden behandeld. Het is echter mogelijk dat uw specifieke reactie op de behandeling of nieuwe bevindingen uw verder deelname aan dit klinisch onderzoek onmogelijk maken. Uw arts zal u van een dergelijke situatie op de hoogte stellen en u adviseren over de op dat moment voor u beste behandeling.

U kunt zich tijdens of na deze studie met verdere vragen of problemen altijd wenden tot de behandelend arts. Ook kunt u advies vragen van een onafhankelijk arts van onze afdeling die niet betrokken is bij het onderzoek.

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Onafhankelijk arts voor eventueel advies

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TOESTEMMINGSVERKLARING
voor deelname aan het wetenschappelijk onderzoek:

Autologe stamcel transplantatie voor patiënten met AL amyloidose.

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

Naam : .....

Adres : .....

Woonplaats : .....

Geboortedatum : .....

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

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

Naam : .....

Functie : .....

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

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