NMSG
Nordic Myeloma Study Group

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Recommendation for allogeneic haematopoietic stem cell transplantation of multiple myeloma. On behalf of NMSG

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Preface

At the NMSG board meeting the 28th of September 2016 we decided to write recommendation for the use of allogeneic hematopoietic stem cell transplantation (allo-SCT) in patients with multiple myeloma.

Allo-SCT is not considered standard treatment of patients with multiple myeloma, however, some patients with poor prognosis may benefit from this treatment.

The NMSG board agreed that treatment with allo-SCT should preferably be done within clinical trials. However, financial support to run a clinical trial with allo-SCT consolidation treatment is difficult to establish.

The NMSG board therefore decided to write recommendation for allo-SCT treatment for those patients where the prognosis of the patients justified the risk of allo-SCT treatment.

The board decided that the recommendation should form the basis for a phase 4 observations trial, where knowledge of allo-SCT could be collected for the benefit of the patients.

The recommendations are planned to be up-dated every second year.

NMSG, March 2017

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2 Glossary of abbreviations - (in alphabetical order)

Auto-SCT	Autologous Stem Cell Transplantation
Allo-SCT	Allogeneic Stem Cell Transplantation
CR	Complete Remission
DLI	Allo-reactive donor lymphocytes
FISH	Fluorescence In Situ Hybridization
FLC	Free Light Chain
GVHD	Graft versus Host Disease
HDM	High-Dose Melphalan
HLA	Human Leukocyte histocompatibility Antigen
IMiDs	Immunomodulatory Drugs
ISS	International Staging System
LDH	Lactate Dehydrogenase
MA	Myeloablative
MM	Multiple Myeloma
MRD	Minimal Residual Disease
NCI	National Cancer Institute
NMA	Non Myeloablative
NMSG	Nordic Myeloma Study group
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Proteasome inhibitor
PR	Partial Response
RIC	Reduced Intensity Conditioning
sCR	Stringent Complete Response
SD	Stable Disease
TRM	Treatment-Related Mortality
VGPR	Very Good Partial Response
WHO	World Health Organization

3 Introduction and rationale

Multiple myeloma

Multiple myeloma is an incurable malignant hematologic disease with an incidence of approximately 5 per 100,000 inhabitants and a median age at presentation of about 65 years [1]. Multiple myeloma is characterised by uncontrolled growth of monoclonal plasma cells (myeloma cells) in the bone marrow and production of a monoclonal immunoglobulin (the M-component). Clinically, multiple myeloma is characterized by bone pain, osteolytic lesions, hypercalcemia, renal damage, anaemia and increased susceptibility to infections [2].

Most hematologists consider multiple myeloma to be incurable, but new data from Arkansas show that the majority of patients, enrolled in treatment strategies including proteasome inhibitors, thalidomide, cisplatin, etoposide, high-dose melphalan (HDM) with hematopoietic stem cell support (Auto-SCT) followed by consolidation and maintenance treatment, have a considerable improved prognosis with a median duration of response of more than 10 years [3]. However, 15% of patients treated with this intensive treatment strategy still have a very poor prognosis and the outcome has not changed during different time periods with introduction of IMiDs and PI [3]. High-risk patients are patients with chemotherapy resistant disease with a median overall survival of less than 2 years [4]. These patients can currently be identified by the high-risk markers elevated LDH, extensive disease stage (ISS stage III) , the presence of cytogenetic abnormalities such as chromosome 1 abnormalities, t(4;14), , t(14;16) and del17p determined by FISH [5] and by gene expression profiling (GEP) based on 70 genes (GEP70) or 5 genes (GEP5) [3;6].

Treatment choices for myeloma patients, frontline treatment

Frontline treatment with HDM and Auto-SCT has been standard of care since the beginning of 1996[7] . Options for up-front induction treatment before Auto-SCT for myeloma patients have changed dramatically since the introduction of the proteasome inhibitors (PI) bortezomib and immunomodulatory drugs (IMiDS) thalidomide and lenalidomide. Incorporation of PI and IMiDS as up-front induction treatment results in high response rates that translate into improved progression free survival (PFS). Maintenance treatment with lenalidomide has shown improvement in PFS as up-front treatment but not among high-risk patients. Meta analyses on improvement in overall survival (OS) for transplant eligible patients show overall survival benefit with a HR for 0.75 for patients receiving lenalidomide maintenance. However, only 30 % of the patients not receiving maintenance treatment were treated with lenalidomide at relape (McCarthy IMW 2017).

Allogeneic stem cell transplantation (allo-SCT) with transplantation of a compatible related or unrelated donor is still an option for cure. Allo-SCT has been used in an attempt to improve long-term survival and several clinical trials have explored the use of allo-SCT as up-front treatment. Our knowledge on

outcome of allo-SCT as front line treatment among high-risk patients is not clear. Outcome of patients with poor prognostic markers have been studied in myeloma patients with HLA-identical siblings, including high B2M, ISS stage III and chromosome 13 abnormalities [8-12]. Kröger et al. treated 73 patients with allogeneic transplantation and found no difference in outcome for patients with the high-risk markers del17p and t(4;14) as compared with patients without high-risk markers [10]. A recent prospective trial by Knop et al. found that among patients with the high-risk cytogenetic markers del13q or del17p upfront autologous HDT followed by allo-SCT significantly improved PFS (ASH 2014; 124: abstract 43) None of these studies included the new drugs in the induction treatment and the use of allo-SCT as up-front treatment is not recommended[13;14] .

Treatment choices for myeloma patients, treatment at relapse

At relapse after first auto-HCT several treatment options are available and include a second auto-HCT, the third generation IMiDs pomalidomide, the second generation PI carfilzomib and immune therapy with the antibodies daratumumab and elotuzumab. Some patients achieve a long PFS after the first auto-SCT and a salvage auto-SCT should be considered for these patients at relapse. However, patients, who suffers from a relapse of disease soon after the first auto-SCT (< 1 to 1½ years), are considered resistant to high-dose melphalan[15;16] and the prognosis of these patients are poor[17]. Two small phase 2 studies on the 3nd generation IMiD, pomalidomide, has recently shown to be effective in a large minority of heavily treated high-risk myeloma with relapsed and refractory disease [18;19]. In these studies, overall response rate among patients with high-risk cytogenetic abnormalities was 32 to 42%. Encouraging data are available from the Aspire study on the PI carfilzomib in patients with 1 to 3 prior treatments including both IMiDs and PI [20]. Although the number of high-risk patients in the study was small, preliminary data strongly indicate that treatment with carfilzomib in combination with lenalidomide and dexamethasone provide complete response (CR) in 41 % of the patients with high beta2-microglobulin (B2M) levels and an adverse cytogenetic profile[20].

The use of immune therapy with monoclonal antibodies (MAb) as a supplement to combination treatment strategies is attractive because the mechanism of action of antibodies is different and presumably less toxic to the hematopoietic stem cells. The presence of the CD38 molecule on almost all myeloma cells makes it a valuable target for antibody treatment. MAb against CD38 provide a broad-spectrum of killing activity and it effectively kills the CD38-expressing tumor cells via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and apoptosis. Preliminary results on bone marrow samples show no difference in the lysis effect by the antiCD38 mAb daratumumab between newly diagnosed or relapsed/refractory patients[21]. No results from randomized studies including mAb treatment on high-risk myeloma are yet available but promising data from phase I and II studies including high-risk patients show an effect of the antibody when used as single agent (ASH 2012 120: Abstract 73). Treatment strategies with PI or IMiDs in combination with antiCD38 monoclonal antibodies for myeloma patients with relapse have shown impression response rates in more than 80% of the patients [22-24].

Salvage treatment with allo-SCT have been employed for patients with and early relapse after first line therapy with HDM or patients with poor cytogenetic features. The conditioning regimes have due to the high treatment related mortality (TRM) changes from myeloablative conditioning, used in the 1990ies, to a reduced-intensity conditioning regime (RIC) and has resulted in a decrease in TRM to 10-15% (ref). These data are supported by new exiting data on allo-SCT from Sweden. Patients suffering from an early relapse were treated with allo-SCT including a new conditioning regime with treosulfan and fludarabin. Three years PFS and OS was 68% and 85%, respectively. A recent study showed that achieving CR from salvage relapse treatment correlated to outcome of allo-SCT [25]. It is therefore essential to achieve an optimal reduction of tumor burden at the time of allo-SCT for a long lasting disease control.

We therefore recommend that younger patient with high-risk disease markers and with a relapse within 18 months from first auto-HDT who has achieved VGPR or CR after salvage treatment could be considered for a consolidation treatment with allo-SCT in an attempt to increase the proportion of long term survivors.

4 Recommendation

Selection of patients

1. Younger patients between 18-65 years
2. Eligible for allo-SCT
3. WHO-performance status 0-2
4. Relapse within 18 months from up-front auto-SCT
5. High-risk at diagnosis or at relapse as determined by the FISH abnormalities del1p, amp1q, t(4;14), t(14;16), t(14;20); del17p or who are high-risk by gen-expression profiling or patients with elevated LDH x 2 at diagnosis and ISSIII disease stage.
6. Pt. achieving VGPR or CR to salvage relapse treatment.
7. A maximum of 3 lines of salvage relapse treatment is used to bring the patient in VGPR or CR
8. In younger patients (<50 years of age) an allo-SCT could be considered for high-risk patients as consolidation treatment after auto-SCT if the patient have achieved VGPR or CR

Patients not eligible for an allo-SCT

1. Life expectancy severely limited by diseases other than multiple myeloma
2. Major surgery within 21 days prior to enrolment.
3. Patients with a history of active malignancy during the past 3 years with the exception of non-melanoma skin cancer or stage 0 cervical carcinoma
4. Patients with active, uncontrolled infections

5. Severe neurological or psychiatric disease
6. Severe cardiac dysfunction: (NYHA classification II-IV, see appendix E); EF< 40%.
7. Severe pulmonary dysfunction: DLC0< 50% or FEV1<40%.
8. Any current CNS involvement
9. HIV positive patients
10. Significant hepatic dysfunction (serum bilirubin or transaminases ≥ 2.0 times normal level)
11. Patients with GFR < 40 ml/min
12. Female patients who are pregnant or breast feeding.
13. Systemic AL amyloidosis
14. Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Relapse salvage treatment

Before the patients should be considered for an allo-SCT we recommend that the response to relapse salvage treatment is as least VGPR or CR and that a maximum of 3 lines of salvage relapse treatment have been used to bring the patient in remission. Salvage relapse treatment may include all active myeloma drugs used in combination or as mono therapy. The important issue is to bring the patient in at least VGPR or CR.

A PET/CT scan can be used for evaluation of response before consolidation treatment with allo-SCT. Radiation therapy is recommended to be used to irradiate any PET positive hotspots before proceeding to consolidation treatment with allo-SCT.

Suggested treatment plan for allogenic hematopoietic stem cell transplantation

The patient should proceed to allo-SCT as soon as a VGPR/CR is achieved. An autologous transplantation could be considered as a salvage treatment to bring the patient in VGPR/CR before an allogeneic transplantation.

Conditioning

Several conditioning regimes are available. The choice of conditioning regime depends on the age of the patients. The allo-conditioning regime is designed at each center according to local practice. Commonly used conditioning regimes are mentioned below.

1. 1. treosulfan and fludarabine as an intermediate conditioning regime.
2. 2. RIC regimes:
    a. FLU (150 mg/m2 total in 5 days) plus MEL (100 mg/m2 once)
3. 3. MA regimes
    a. MEL110 + TBI10

Graft versus Host Disease Prophylaxis

GVHD prophylaxis varies according to the co-morbidity of the patients and the donor type, related or unrelated donor. The GVHD prophylaxis is designed at each center according to local practice.

Post-transplant therapy with DLI, IMiDs, proteasome inhibitors, or monoclonal antibodies.

Maintenance treatment after consolidation treatment with allo-SCT consolidation is at the treating physician discretion. Monitoring patients for minimal residual disease (MRD), GVHD and chimerism post-allo-SCT provide the treating physician with guidance to treat patients with alloreactive donor lymphocytes (DLI). In patients that are MRD positive and where donor chimerism are declining a DLI could be considered. Maintenance treatment with IMiDS, proteasome inhibitor (PI) or monoclonal antibodies used as monotherapy or in combination depends on 1: state of remission; 2: whether the patient´s disease have demonstrated sensitivity to these drugs and 3: whether or not the patient has GVHD. Maintenance treatment with IMiDS is usually started 3 months after the Allo-SCT and in reduced dose.

Minimal residual disease (MRD)

Allo-SCT is an intensive treatment with many side effects due to GVH disease. In order to properly evaluate the clinical benefit of the treatment is utterly important to assess minimal residual disease (MRD) in patients. In multiple myeloma achievement of minimal residual disease (MRD)-negative status, as determined by multiparametric flow cytometry or molecular techniques, is associated with improved outcome both in the setting of standard-risk and high-risk cytogenetics. MRD-negative disease will probably become an important endpoint in clinical studies and a surrogate marker for survival.

MRD assessment is recommended by use of multiparametric flow cytometry (MFC), or by molecular techniques such as VDJ sequencing or allele-specific oligonucleotide PCR. Patients with evidence of immunofixation negative CR at a response evaluation moment should be studied for MRD every 3 months.

Serum samples are recommended to be tested for free-light chains. In addition to measuring the absolute levels of free-light chain, the free-light chain ratio will be considered (normal reference range, 0.26 to 1.65). Patients with a k/l FLC ratio <0.26 are typically defined as having a monoclonal lambda free light chain and those with ratios >1.65 are defined as having a monoclonal kappa free light chain. Bone marrow samples will be tested by 8-colour flowcytometry for the presence of monoclonal plasma cells according to international standards. The outcome of patients in stringent CR or MFC remission will be compared with those in immunofixation negative CR or VGPR.

5 Appendix A; lines of therapy

Guidelines for the determination of the number of prior lines of therapy in multiple myeloma.
Based on Rajkumar et al (23)

Line of Therapy

A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (e.g., 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by stem cell transplantation consolidation, and lenalidomide maintenance is considered 1 line).

New line of Therapy

A treatment is considered a new line of therapy if any 1 of the following 3 conditions are met:

1. *Start of a new line of treatment after discontinuation of a previous line*.

If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. A regimen is considered to have been discontinued if all the drugs in that given regimen have been stopped. A regimen is not considered to have been discontinued if some of the drugs of the regimen, but not all, have been discontinued.
The reasons for discontinuation, addition, substitution, or SCT do not influence how lines are counted. It is recognized that reasons for change may include end of planned therapy, toxicity, progression, lack of response, inadequate response.

2. *The unplanned addition or substitution of 1 or more drugs in an existing regimen.*

Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.

3. *Stem cell transplantation (SCT):*

In patients undergoing >1 SCT, except in the case of a planned tandem SCT with a predefined interval (such as 3 months), each SCT (autologous or allogeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different. It is recommended that data on type of SCT also be captured.
Planned tandem SCT is considered 1 line. Planned induction and/or consolidation, maintenance with any SCT (frontline, relapse, autologous or allogeneic) is considered 1 line.

Interruptions and dose modifications

- If a regimen is interrupted or discontinued for any reason and the same drug or combination is restarted without any other intervening regimen, then it should be counted as a single line.
- However, if a regimen is interrupted or discontinued for any reason, and then restarted at a later time point but 1 or more other regimens were administered in between, or the regimen is modified through the addition of 1 or more agents, and then it should be counted as 2 lines.
  - Modification of the dosing of the same regimen should not be considered a new line of therapy.

6 Appendix B; relapsed and refractory myeloma

Definition of Relapsed and Refractory Myeloma. Adapted from Rajkumar VS et al. (24)

Refractory Myeloma:

Refractory myeloma is defined as disease that is non-responsive (failure to achieve minimal response or develops PD while on therapy) while on primary or salvage therapy, or progresses within 60 days of last therapy. There are 2 categories of refractory myeloma.

- Relapsed and refractory myeloma: Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously to then progressing in their disease course.
- Primary refractory myeloma: refractory myeloma is defined as disease that is non- responsive in patients who have never achieved minimal response or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression; as well as primary refractory, progressive disease where patients meet criteria for true progressive disease.

Relapsed myeloma

Relapsed myeloma is defined as previously treated myeloma which progresses and requires the initiation of salvage therapy but does not meet the criteria for either primary refractory myeloma or relapsed and refractory myeloma

7 Appendix C; response criteria

Response criteria, adapted from updated International Myeloma Working Group Response Criteria

Response	IMWG criteria
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow. • A normal FLC ratio of 0.26–1.65 is required. **Two consecutive assessments are needed**
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 colour flow cytometry **Two consecutive assessments of laboratory parameters are needed**
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analysed by multi-parametric flow cytometry (with>four colours)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h. **Two consecutive assessments are needed**

PR	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required **Two consecutive assessments are needed. No known evidence of progressive disease or new bone marrow lesions if radiographic studies were performed**
MR for relapse refractory myeloma only	≥25% but ≤ 49% reduction in serum M-protein and reduction in 24h urine M-protein by 50-89%, which still exceed 200mg/24H. If present at baseline, 25-49% reduction in size of soft tissue plasmacytomas; no increase in size or number of lytic bone lesions(development of compression fracture does not exclude response)
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease • No known evidence of progressive disease or new bone marrow lesions if radiographic studies were performed
Progressive disease	Increase of ≥25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥0.5 g/dL)4 and/or • Urine M-component (the absolute increase must be ≥200 mg/24 h) and/or • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase (≥25%) in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder **Two consecutive assessments before new therapy are needed.**
Abbreviations: CR, complete response ; FLC, free light chain; M, monoclonal; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.	

Definite increase in the size of existing bone lesions or soft tissue plasmacytomas is defined as below: ≥25% increase in the size of at least one bidimensionally measurable lesion (in comparison with the measurements at Nadir) or appearance of a new lesion. Pathological fracture or collapse of bone is not necessarily evidence of disease progression.

8 Appendix D; Zubrod-ECOG-Who Performance Status Scale

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
5	Death

9 Appendix E; NYHA

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE (NYHA)

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association, Inc.: Diseases of the heart and blood vessels; Nomenclature and criteria for diagnosis, 6th Ed. Boston: Little, Brown; 1964.

Summary:

Grade 1 No breathlessness

Grade 2 Breathlessness on severe exertion

Grade 3 Breathlessness on mild exertion

Grade 4 Breathlessness at rest

10 Appendix F; R-ISS

R-ISS stage	Criteria
I	• Serum ß2 microglobulin < 3,5 md/L and serum albumin ≥ 3,5 g/dL and • Standard chromosomal abnormalities by iFISH and • LDH within normal range
II	• Not R-ISS stage I or III
III	• Serum ß2 microglobulin ≥ 5,5 mg/L **and** either high-risk chromosomal abnormalities** or high LDH

* No high-risk chromosomal abnormalities

** Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)

Palumbo et al. 2015 [26]

11 Apendix G; Acute GVH disease

GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE

Severity of Individual Organ Involvement

Skin	+1	a maculopapular eruption involving less than 25% of the body surface
	+2	a maculopapular eruption involving 25-50% of the body surface
	+3	generalized erythroderma
	+4	generalized erythroderma with bullous formation and often with desquamation
Liver	+1	bilirubin (2.0-3.0 mg/100 ml)
	+2	bilirubin (3-5.9 mg/100 ml)
	+3	bilirubin (6-14.9 mg/100 ml)
	+4	bilirubin > 15 mg/100 ml
Gut		Diarrhea is graded +1 to +4 in severity. Nausea and vomiting and/or anorexia caused by GVHD is assigned as +1 in severity The severity of gut involvement is assigned to the most severe nvolvement noted Patients with visible bloody diarrhea are at least stage +2 gut and grade +3 overall
Diarrhea	+1	≤ 1000 ml of liquid stool/day* (≤ 15ml of stool/kg/day)†
	+2	>1,000 ml of stool/day* (> 15ml of stool/kg/day)†
	+3	>1,500 ml of stool/day* (> 20ml of stool/kg/day)†
	+4	2,000 ml of stool/day* (≥ 25ml of stool/kg/day)†

*In the absence of infectious/medical cause
†For pediatric patients

Severity of GVHD

Grade I	+1 to +2 skin rash No gut or liver involvement
Grade II	+1 to +3 skin rash +1 gastrointestinal involvement and/or +1 liver involvement
Grade III	+2 to +4 gastrointestinal involvement and/or +2 to +4 liver involvement with or without a rash
Grade IV	Pattern and severity of GVHD similar to grade 3 with extreme constitutional symptoms or death

[a] From "Graft-vs-host disease" Sullivan, Keith M. *Hematopoietic Cell Transplantation* Ed: D. Thomas, K. Blume, S. Forman, Blackwell Sciences; 1999, pages 518-519

12 Appendix H; chronic GVH disease

CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD)

Chronic GVHD in allogeneic transplant recipients resembles autoimmune disorders such as scleroderma, Sjogren syndrome, primary biliary cirrhosis, lichen planus, wasting syndrome, bronchiolitis obliterans among others manifestations (see below). Approximately 50% of patients will develop this complication within 6 months after the transplant despite continued treatment with immunosuppressive medications. Close monitoring is recommended during the first 2 years after allogeneic stem cell transplantation so that appropriate treatment can be instituted promptly in patients who develop chronic GVHD. Debilitation, joint contractures and profound immunosuppression resulting in recurrent bacterial infections are prominent characteristics of untreated chronic GVHD.

A. Classification of Chronic GVHD

The purpose of this classification is to identify patients with cGVHD who need long-term systemic immunosuppression according to clinical and laboratory findings and risk factors at the time of initial diagnosis. In addition, a morbidity scale has been developed to help grade the severity of manifestation of chronic GVHD (Appendix D) at the time of diagnosis, when changes in treatment are made and when assessing treatment response.

1. Chronic GVHD not requiring systemic treatment: mild abnormalities involving a single site, with platelet count >100,000 and no steroid treatment at the onset of chronic GVHD

a) Oral abnormalities consistent with cGVHD, a positive skin or lip biopsy, and no other manifestations of cGVHD
b) Mild liver test abnormalities (alkaline phosphatase ≤2 x upper limit of normal, AST or ALT ≤3 x upper limit of normal and total bilirubin ≤1.6) with positive skin or lip biopsy, and no other manifestations of cGVHD
c) Less than 6 papulosquamous plaques, macular-papular or lichenoid rash involving <20% of body surface area (BSA), dyspigmentation involving <20% BSA, or erythema involving <50% BSA, positive skin biopsy, and no other manifestations of cGVHD
d) Ocular sicca (Schirmer's test ≤5mm with no more than minimal ocular symptoms), positive skin or lip biopsy, and no other manifestations of cGVHD
e) Vaginal or vulvar abnormalities with positive biopsy, and no other manifestations of cGVHD

2. Chronic GVHD requiring systemic treatment: more severe abnormalities or involvement of multiple sites, or platelet count <100,000, or steroid treatment at the onset of chronic GVHD

a) Involvement of two or more organs with symptoms or signs of cGVHD, with biopsy documentation of cGVHD in any organ
b) ≥15% base line body weight loss not due to other causes, with biopsy documentation of cGVHD in any organ
c) Skin involvement more extensive than defined for clinical limited cGVHD, confirmed by biopsy
d) Scleroderma or morphea
e) Onycholysis or onychodystrophy thought to represent cGVHD, with documentation of cGVHD in any organ
f) Decreased range of motion in wrist or ankle extension due to fasciitis caused by cGVHD
g) Contractures thought to represent cGVHD
h) Oral involvement with functional impairment, refractory to topical treatment
i) Vaginal involvement with functional impairment, refractory to topical treatment
j) Bronchiolitis obliterans not due to other causes
k) Positive liver biopsy; or abnormal liver function tests not due to other causes with alkaline phosphatase >2 x upper limit of normal, AST or ALT >3 x upper limit of normal, or total bilirubin >1.6, and documentation of cGVHD in any organ
l) Positive upper or lower GI biopsy
m) Fasciitis or serositis thought to represent cGVHD and not due to other causes

B. Physical manifestations of Chronic GVHD
Manifestations that are distinctive for chronic GVHD can begin before day 100 after the transplant, and manifestations that are typical of acute GVHD can persist long after day 100. For this reason, the differential diagnosis between acute and chronic GVHD cannot be made solely according to the time interval from transplant. The diagnosis of chronic GVHD requires at least one manifestation that is distinctive for chronic GVHD (*identified by italic print below*) as opposed to acute GVHD. In all cases, infection and others causes must be ruled out in the differential diagnosis of chronic GVHD.

Karnofsky or Lansky Clinical Performance scores <60%, ≥15% weight loss, and recurrent infections are usually signs of clinical extensive chronic GVHD. Abnormalities that could indicate chronic GVHD are categorized by organ system are listed below (*italic print identifies manifestation more distinct of chronic GVHD):*

Skin	Erythema, dryness, pruritis, macular-papular or urticarial rash, *pigmentary changes (i.e., hyperpigmentation, vitiligo), mottling, papulosquamous or lichenoid plaques, hyperkeratosis, exfoliation (ichtyosis), nodules, scleroderma, morphea (one or several circumscribed, indurated and shiny lesions)*. The extent of skin involvement and the skin thickness score for patients with scleroderma needs to be recorded at the time of diagnosis, when changes in treatment are made and when assessing treatment response. Medical photos are also useful for assessing the extent of skin involvement and response to treatment.
Nails	B. Ridging, onychodystrophy, onycholysis
Hair	*Premature graying (scalp hair, eyelashes, eyebrows), thinning scalp hair, alopecia, decreased body hair*
Mouth	Dryness, burning, gingivitis, mucositis, striae, *dryness, atrophy, erythema, lichenoid changes, ulcers, labial atrophy or pigmentary changes, tightness around the mouth, sensitivity to acidic, strong flavors, heat or cold, tooth decay*
Eyes	*Dryness, burning, blurring, gritty eyes, photophobia, pain*
Vagina/vulva	*Dryness, dyspareunia, stricture or stenosis, erythema, atrophy or lichenoid changes not induced by ovarian failure or other causes*
Liver	Jaundice and elevated liver function tests not due to other causes (see laboratory tests)
Lung	*Bronchiolitis obliterans (see diagnostic indicators), cough, wheezing, dyspnea on exertion, history of recurrent bronchitis or sinusitis*
GI	Anorexia, nausea, vomiting, diarrhea, *malabsorption, dysphagia, odynophagia*
Myofascial	*Stiffness and tightness with restriction of movement, occasionally with swelling, pain, cramping, erythema and induration, most commonly affecting the forearms, wrists and hands, ankles, legs and feet, inability to extend the wrists without flexing the fingers or the elbows, contractures*
Muscle	Proximal muscle weakness, cramping
Skeletal	*Arthralgia of large proximal girdle joints and sometimes smaller joints*
Serosal	*Unexplained effusions involving the pleural, pericardial, or peritoneal cavities not due to venocclusive disease of the liver, cardiac insufficiency, malignancy, infection, GM-CSF toxicity or other causes*

C. Laboratory Testing and Diagnostic Indicators of Chronic GVHD

Eye	*Schirmer's test with a mean value ≤ 5 mm at 5 minutes, or values of 6-10 mm in patients who have sicca symptoms, or keratitis detected by slit lamp examination*
Liver	Elevated liver function tests not due to other causes (alkaline phosphatase ≥2 x upper limit, of normal, AST or ALT >3 x upper limit of normal or total serum bilirubin ≥1.6)
Lung	*New obstructive lung defect defined as an FEV1 <80% of predicted with either an FEF 25-75 <65% of predicted or RV >120% of predicted, or a decrease of FEV1/FVC by >12% within a period of less than 1 year, thought not to be caused by an infectious process, asthma or recurrent aspiration from the sinuses or from gastroesophageal reflux. In the absence of GVHD in any other organ, the diagnosis of bronchiolitis obliterans requires negative microbiological tests from bronchoalveolar lavage, evidence of air trapping by high resolution end-expiratory and end-inspiratory CAT scan of the lungs, or confirmation by thoracoscopic biopsy.*
Esophagus	*Esophageal web formation, stricture or dysmotility demonstrated by barium swallow, endoscopy or manometry*
Intestine	Endoscopic findings of mucosal edema and erythema or focal erosions with histological changes of apoptotic epithelial cells and crypt cell drop out. Patients with unresolved acute GVHD may have more severe intestinal mucosal lesions including ulcers and mucosal sloughing.
Muscle	*Elevated CPK or aldolase, EMG findings consistent with myositis with biopsy revealing no other etiological process*
Blood	Thrombocytopenia (usually 20,000-100,000/□l), eosinophilia (> 0.4 x 10^3/uL), hypogammaglobulinemia. Hypergammaglobulinemia and autoantibodies occur in some cases.

13 Reference List

Reference List

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