

Indications for High-Dose Chemotherapy with Autologous Stem Cell Support in Patients with Systemic Amyloid Light Chain Amyloidosis

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Systemic amyloid light chain amyloidosis is a protein conformation disorder caused by a clonal plasma cell dyscrasia. Symptoms result from fibrillar extracellular deposits in kidney, heart, liver, gut, peripheral nervous system and other tissues. The deposits disrupt organ function and ultimately lead to death. The prognosis of systemic amyloid light chain (AL) amyloidosis is poor; less than 5% of all patients survive 10 years or longer. Using conventional chemotherapy, the median survival could be prolonged by 4 months. Treatment with high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT) of selected patients has been shown to arrest and even to reverse the disease course. This procedure however remains controversial because treatment related mortality (TRM) in AL amyloidosis is substantially higher (15–40%) than in multiple myeloma (<5%). Here we review recent results of ASCT, eligibility criteria for HDM and report our own treatment results in 41 patients.

Keywords: Amyloid light chain, High-dose melphalan, Autologous stem cell transplantation, Treatment-related mortality.

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Indication and Patient Selection for High-dose Melphalan (HDM) and Autologous Stem Cell Transplantation (ASCT)

Based on the success of ASCT in multiple myeloma (1) some institutions have begun to apply this treatment modality to patients (pts) with amyloid light chain (AL) amyloidosis. Indication for ASCT is systemic disease excluding pts with isolated carpal tunnel syndrome or skin involvement and other localized forms. Table 1 shows the results of single- and multicenter studies (listing only the latest publication from each center). Encouraging hematological remission and organ response rates have been reported. On the other hand treatment-related mortality (TRM) beyond 20% has been ob-

served. Advanced cardiac disease (10, 15), reduced renal function (16), more than two organs involved (17), severe hypotension (<90 mmHg) and poor WHO performance status (8) are risk factors for increased TRM after HDM and ASCT. Therefore patient selection plays a crucial role in the decision for that treatment. The results of the largest patient group have been reported by Skinner et al. (10). Out of 701 patients with AL amyloidosis, 394 were considered eligible for HDM and ASCT. In this group, 82 patients did not proceed to HDM because of their own decision or disease progression. The median survival of 312 patients treated with HDM was 4.6 years. A hematological complete remission (CR) was achieved in 40% of pts evaluable at one year after ASCT, and was associated with prolonged survival. Significantly higher organ response rates were observed in these pts (66% vs. 30% in CR vs. non-CR, $P < 0.001$). The disappearance of the monoclonal plasma cells after HDM is correlated with melphalan dosage used. Risk factor for TRM was symptomatic cardiac involvement. Survival, CR rate, and organ function improvement were higher for transplanted pts compared to the results of any other therapy. Pretreatment with 2 cycles of oral melphalan/prednisone before transplantation did not improve results in a prospective randomized trial (18). Furthermore, superior survival in pts undergoing HDM and ASCT was observed in a case-control study reported by the Mayo Group (19). Sixty-three patient pairs had been matched for age, sex, time to clinical presentation, left ventricular ejection fraction, serum creatinine, septum thickness, nerve in-

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TABLE 1. Results of single- and multicenter studies of HDM and ASCT in patients with AL amyloidosis

Reference	Patients transplanted	TBI conditioning	Melphalan dosage	TRM %	Median follow-up (months)	Hematologic complete remission (patients)	Organ response (%) ^b	OS at 1 year (%)	OS at >2 years (%)
Single-center clinical trials									
Reich 2001 (2)	4	ND	140-200	2 patients	NA	1	2 patients	2 patients	NA
Lachmann 2003 (3)	55	ND	NA	22	20	NA	NA	NA	NA
Van Gameren 2002 (4)	11	ND	NA	NA	25	0/9	67	NA	75
Blum 2003 (5)	12	All patient(s) 5.5 Gy	Not given	15	24 for patients alive	3/11	50	66	47
Gertz 2004 (6)	171	17/171	100-200	12	NA	115/150 ^a	NA	NA	NA
Knop 2004 (7)	7	ND	100-140	29	12 for patients alive	NA	NA	NA	NA
Mollee 2004 (8)	20	2/20	140-200	35	18 for patients alive	5/11	NA	NA	56 (3 years)
Perz 2004 (9)	24	ND	100-200	13	31	11/21	NA	84	84
Skinner 2004 (10)	277	NA	100-200	13	NA	73/181	44	79	47 (5 years)
Total	591			Median: 14% ^c		Median: 40% ^d			
Multicenter clinical trials									
Moreau 1998 (11)	21	3/21 12 Gy	140-200	43	14	3/12	83	NA	57 (4 years)
Gillmore 1999 (12)	40	ND	100-200	38	12 for patients alive	10/25	56	60	NA
Vesole 2003 (13)	114	9/114	NA	25	29	13/40 ^a	36	68	57 (3 years)
Gertz 2004 (14)	28	ND	200	14	30 for patients alive	NA	75	86	62 (3 years)
Total	201			Median: 32% ^c					

NA, not available; ND, not done.

^a Complete remission + partial remission.

^b Of evaluable patients.

^c Median in percent was only taken from studies which included more than 10 transplanted patients.

^d Median in percent was only taken from studies which included more than 10 transplanted patients and outlined CR rate.

involvement, 24-hour urine protein excretion, and serum alkaline phosphatase. Sixteen pts treated with HDM and 50 control pts died. Comparing the HDM and the control group, the 1-, 2-, and 4-year overall survival (OS) rates were significantly different (89% and 71%; 81% and 55%; and 71% and 41%; $P < 0.001$). These results underline the importance of high-dose therapy in the treatment of AL amyloidosis. On the other hand, eligibility for HDM is a favorable prognostic factor for OS of pts not undergoing HDM (20). To further evaluate the role of ASCT, a French prospective randomised clinical phase III study comparing melphalan-dexamethasone with HDM is under way, but has not been finished yet (21).

A number of different risk-adapted approaches to assess eligibility for HDM and ASCT have been published recently. In one report (17), patients were classified in three risk groups (good-intermediate-poor). Good-risk pts could be of any age, had 1 or 2 organs involved, no signs of cardiac disease and a creatinine clearance ≥ 51 ml/min. Intermediate risk pts were younger than 71 years, had 1 or 2 organs involved (either cardiac disease or creatinine clearance ≤ 51 ml/min) and only asymptomatic or compensated heart disease. Poor risk pts had more than 2 organs involved or advanced cardiac disease. In this approach melphalan dosages were based on the risk group and age. For poor risk pts HDM and ASCT was not recommended. The Boston Group algorithm (10) included pts up to the age of 80 y. Pts were ineligible for HDM if they

had decompensated congestive heart failure, cardiac ejection fraction $< 40\%$, persistent pleural effusions, systolic blood pressure ≤ 90 mm Hg, O_2 saturation $< 95\%$ by room air or a performance status ≥ 3 . The melphalan dosage depended on age, cardiac ejection fraction and number of collected stem cells. The British Guidelines for diagnosis and management of AL amyloidosis (22) recommended HDM and ASCT only for good-risk pts (17) who are refractory or relapsed after initial therapy. The Italian GITMO transplants pts younger than 60 y, with no more than 2 organs involved and without severe heart involvement (23). At our institution exclusion criteria for HDM and ASCT are age beyond 70 y, symptomatic heart involvement with NYHA stage III or IV and WHO performance status > 2 (3 if due to PNP).

Own Treatment Results

We have treated 41 pts with HDM and ASCT between 1998 and 2004. Thirty-seven pts had AL amyloidosis and 4 pts multiple myeloma stage III with AL amyloidosis. Patient characteristics are summarized in Table 2. All pts had received mobilization chemotherapy and 40 out of 41 have been pretreated with VAD, dexamethasone or melphalan/prednisone (Table 2 and (9)). Melphalan dosage was adapted to creatinine clearance and was reduced in pts older than 65 y or with symptomatic cardiac disease. CR was obtained in 16 out of 32 (50%) and organ response was observed in 15 out of 37

TABLE 2. Patient characteristics

Patients transplanted	41
Time from diagnosis to transplant (months)	9 (2-123) ^a
Male/female	23/18
Age at ASCT (years)	56 (34-69) ^a
Light chain isotype: lambda/kappa	34/7
Organs involved	2 (1-5) ^a
Patients with cardiac involvement	24
Patients with kidney involvement/hemodialysis at ASCT	27/5
Patients with creatinine >2 mg/dl at ASCT	11
Patients with pretreatment with VAD/dexamethasone/MP	24/6/10
Stem cell mobilisation chemotherapy with ifosfamide 12 g/m ² +G-CSF	14 pts
Cyclophosphamide 4 g/m ² +G-CSF	4 pts
CAD ^b +G-CSF	22 pts
Other	1 pt
Hematological remission status at ASCT: CR/PR/SD progression	4/7/23/1
Melphalan dose 200/140/100 mg/m ²	23/9/9 ^c
Follow-up since HDM (months)	24 (0-77) ^a
Comenzo/Gertz risk categories: good/intermediate/poor	13/4/24
Skinner eligibility algorithm: eligible/not eligible	35/6

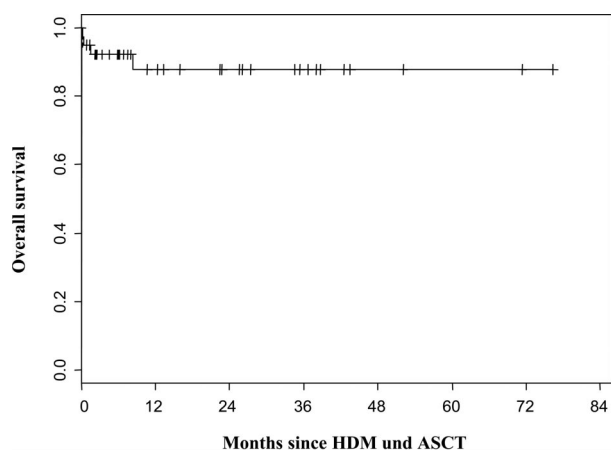
^a Median (range).

^b CAD = cyclophosphamide 1 g/m², adriamycin 60 mg/m², and dexamethasone 40 mg for 4 days.

^c Dose reduction: age: 2 pts; creatinine clearance < 60 ml/min: 12 pts; advanced cardiac disease: 4 pts.

pts evaluable (40%). In further 18 pts organ function was stabilized (49%). Thirty-seven out of 41 pts are alive after a median observation of 24 months since HDM. The TRM was 7%. However, this rather low rate is not a result of a very restrictive patient selection (Table 2). One patient died of cardiac failure due to AL amyloidosis 8 months after ASCT. The OS rate at 2 y is 89% (Fig. 1).

Currently we investigate the toxicity and efficacy of pulsed high-dose dexamethasone as induction therapy prior to HDM and ASCT in a phase II study.

**FIGURE 1.** Overall survival after HDM and ASCT

Summary

HDM is currently the treatment of choice for pts who are eligible to undergo this treatment. Long-term survival has been significantly improved for pts who achieve a CR after HDM. Supportive therapy of cardiac and renal disease plays a substantial role in the treatment of these pts. Providing a network of different medical specialists with expertise in the field of AL amyloidosis within the same centre is important for the optimal care for these pts and may lead to a further reduction of TRM. Treatment of pts who are not eligible for high-dose chemotherapy and of pts with persistent or relapsed clonal disease after transplantation is still a challenge. For these pts new drugs (bortezomib, lenalidomide) have to be tested in clinical studies.

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REFERENCES

- Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* 2004; 351: 1860.
- Reich G, Held T, Siegert W, et al. Four patients with AL amyloidosis treated with high-dose chemotherapy and autologous stem cell transplantation. *Bone Marrow Transplant* 2001; 27: 341.
- Lachmann HJ, Gillmore JD, Pepys MB, et al. Outcome in systemic AL amyloidosis following stem cell transplantation or infusional chemotherapy. *Blood* 2002; 788.
- Van Gameren II, Hazenberg BP, Jager PL, et al. AL amyloidosis treated with induction chemotherapy with VAD followed by high dose melphalan and autologous stem cell transplantation. *Amyloid* 2002; 9: 165.
- Blum W, Khoury H, Lin HS, et al. Primary amyloidosis patients with significant organ dysfunction tolerate autologous transplantation after conditioning with single-dose total body irradiation alone: a feasibility study. *Biol Blood Marrow Transplant* 2003; 9: 397.
- Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. *Bone Marrow Transplant* 2004; 34: 1025.
- Knop S, Lengerke C, Hebart H, et al. High-dose melphalan followed by autologous stem cell transplantation in patients with primary systemic (AL) amyloidosis. *Onkologie* 2004; 27 (Suppl. 3): 186.
- Mollee PN, Wechalekar AD, Pereira DL, et al. Autologous stem cell transplantation in primary systemic amyloidosis: the impact of selection criteria on outcome. *Bone Marrow Transplant* 2004; 33: 271.
- Perz J, Schonland SO, Hundemer M, et al. High-dose melphalan with autologous stem cell transplantation after VAD induction chemotherapy for treatment of AL amyloidosis: a single centre prospective phase II study. *Br J Haematol* 2004; 127: 543.
- Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med* 2004; 140: 85.
- Moreau P, Leblond V, Baurquelot P. Prognostic factors of survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. *Br J Haematol* 1998; 101: 766.
- Gillmore JD, Apperley JF, Craddock C. High dose melphalan and stem cell rescue for AL amyloidosis. In: Kyle, RA, Gertz MA, eds. *Amyloid and Amyloidosis*. Pearl River, NY: Parthenon Publishing; 1999: 102.
- Vesole D, Perez WS, Reece DE, et al. High Dose Therapy with Autologous Hematopoietic Stem Cell Transplantation (HSCT) for Patients with Primary Systemic Amyloidosis (AL): Results from the Autologous Blood and Marrow Transplant Registry (ABMTR). *Blood* 2003; 102: 402.
- Gertz MA, Blood E, Vesole DH, et al. A multicenter phase 2 trial of stem cell transplantation for immunoglobulin light-chain amyloidosis (E4A97): an Eastern Cooperative Oncology Group Study. *Bone Marrow Transplant* 2004; 34: 149.

15. Dispenzieri A, Gertz MA, Kyle RA, et al. Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. *Blood* 2004; 104: 1881.
16. Gertz MA, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for the management of primary systemic amyloidosis. *Am J Med* 2002; 113: 549.
17. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 2002; 99: 4276.
18. Santhorawala V, Wright DG, Seldin DC, et al. High-dose intravenous melphalan and autologous stem cell transplantation as initial therapy or following two cycles of oral chemotherapy for the treatment of AL amyloidosis: results of a prospective randomized trial. *Bone Marrow Transplant* 2004; 33: 381.
19. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplant: A case control study. *Blood* 2004; 103: 3960.
20. Dispenzieri A, Lacy MQ, Kyle RA, et al. Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. *J Clin Oncol* 2001; 19: 3350.
21. Jaccard A, Moreau P, Leblond V, et al. Best therapy for primary amyloidosis, a not-yet-solved question. *Blood* 2004; 104: 2990.
22. Bird J. Guidelines in the diagnosis and management of AL amyloidosis. *Br J Haematol* 2004; 125: 681.
23. Barosi G, Boccadoro M, Cavo M, et al. Italian Society of Hematology; Italian Society of Experimental Hematology; Italian Group for Bone Marrow Transplantation. Management of multiple myeloma and related disorders: guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO). *Haematologica* 2004; 89: 717.