Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach

Giovanni Palladini,[1] Paolo Milani,[1,2] Andrea Foli,[1] Laura Obici,[1] Francesca Lavatelli,[1] Mario Nuvolone,[1] Riccardo Caccialanza,[3] Stefano Perlini,[1,2] and Giampaolo Merlini[1]

[1]Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy and Department of Molecular Medicine, University of Pavia; [2]Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo and University of Pavia; [3]Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

ABSTRACT

The combination of oral melphalan and dexamethasone is considered standard therapy for patients with light-chain amyloidosis ineligible for autologous stem cell transplantation. However, previous trials reported different rates of response and survival, mainly because of the different proportions of high-risk patients. In the present study, including a total of 259 subjects, we treated 119 patients with full-dose melphalan and dexamethasone (dexamethasone 40 mg days 1-4), and 140 patients with advanced cardiac disease with an attenuated dexamethasone schedule (20 mg). Hematologic response rates were 76% in the full-dose group and 51% in the patients receiving the attenuated schedule; the corresponding complete response rates were 31% and 12%, respectively. The median survival was 7.4 years in the full-dose group and 20 months in the attenuated-dose group. Use of high-dose dexamethasone, amino-terminal pro-natriuretic peptide type-B >1800 ng/L, a difference between involved and uninvolved free light chains of >180 mg/L, troponin I >0.07 ng/mL, and response to therapy were independent prognostic determinants. In relapsed/refractory subjects bortezomib combinations granted high hematologic response rates (79% and 63%, respectively), proving the most effective rescue treatment after melphalan and dexamethasone. In summary, melphalan plus dexamethasone was highly effective with minimal toxicity, confirming its central role in the treatment of AL amyloidosis. Future randomized trials will clarify whether bortezomib is best used in frontline combination with melphalan and dexamethasone or as rescue treatment.

Introduction

In 2004, the introduction of oral melphalan and dexamethasone (MDex) in the treatment of AL amyloidosis offered patients who were too frail to undergo autologous stem cell transplantation (ASCT) a viable alternative that could grant a high response rate and prolonged survival.[1,2] Subsequently, a multicenter randomized trial from a French group failed to demonstrate an advantage in terms of response rate and survival for patients undergoing ASCT over those receiving MDex.[3] However, these trials were designed before the era of biomarker-based risk stratification and evaluation of response, which are now considered essential in the management of AL amyloidosis.[4] Other studies that included a greater proportion of subjects with advanced cardiac involvement had less encouraging results, with a lower rate of response and shorter survival.[5-7]

Oral MDex has been adopted as standard treatment for AL amyloidosis in several referral centers.[8-16] At our center, MDex was offered to all patients with AL amyloidosis who did not satisfy eligibility criteria for ASCT between 2004 and 2009.[10] To increase the tolerability of this regimen, the dose of dexamethasone was reduced in subjects with advanced disease. More recently, novel agents, such as lenalidomide[17-22] and, particularly, bortezomib,[23,24] gave very promising results in combination with alkylators in small phase II studies or retrospective series, and a randomized and stratified phase III trial is ongoing in Europe and Australia to compare MDex with the combination of bortezomib and MDex (BMDex) (*www.clinicaltrials.gov NCT01277016*). The results of this trial are eagerly awaited, but will not be available for at least 2 years. Nevertheless, although the safety and efficacy of these combinations and of standard treatment have not been formally compared, there is an increasing tendency to treat patients with AL amyloidosis with bortezomib, steroid, and alkylators frontline.

Thus, pending the results of clinical trials, there is the need for large studies assessing the safety and efficacy of the current standard of care according to recent standards, including risk stratification and evaluation of response based on cardiac biomarkers and free light chain (FLC) measurements. In the present study we report the outcome of risk-adapted MDex in 259 consecutive patients with AL amyloidosis who were treated at our center between 2004 and 2009.

Methods

Between 2004 and 2009, all the patients with AL amyloidosis newly diagnosed at the Pavia Amyloidosis Research and Treatment Center

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Correspondence: gmerlini@unipv.it

who were not candidates for ASCT were treated with MDex and were included in the study. The patients gave written informed consent as approved by institutional Ethics Committee. The amyloid deposits were characterized as AL-type by immuno-electron microscopy or proteomics in all cases.[25] Evidence of a monoclonal component of the same isotype as that identified in the amyloid fibrils at serum and urine immunofixation electrophoresis and/or an abnormal FLC κ/λ ratio was required.[26] Subjects with lytic bone lesions were excluded.

Eligibility criteria for ASCT have been previously described[10] and are detailed in the *Online Supplementary Material*. Patients who had potentially reversible contraindications to ASCT received a stem cell-sparing regimen: high-dose dexamethasone alone or combined with thalidomide before 2007, and the combination of cyclophosphamide, thalidomide, and dexamethasone (CTD) thereafter.[27-29]

The patients received oral melphalan (0.22 mg/Kg) and dexamethasone (40 mg/day) on days 1-4 in 28-day cycles.[1] The toxicity of high-dose dexamethasone in AL amyloidosis is not negligible, the most common concerns being fluid retention and arrhythmias.[27,30] Thus, patients with repetitive ventricular arrhythmias[31] and/or fluid retention >3% of body weight (referring to usual non-edematous body weight)[32,33] received attenuated MDex, with dexamethasone 20 mg/day. Melphalan was reduced by 25% in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. The maximum allowed number of cycles was nine. Treatment was discontinued in the case of toxicity, in the event a complete response or any hematologic response plus organ response was obtained after cycle 6, or in the case hematologic response was not reached by cycle 3. In this last case, patients were switched to alternative treatments in order to spare unnecessary toxicity and with the aim of obtaining an adequate response to second-line therapy. All the patients achieving at least a partial response after cycle 3 continued treatment. Best hematologic response was achieved after a median of 3.8 months (range, 3-10 months) and three cycles (range, 3-9 cycles) of MDex.

Hematologic response was assessed 3 months after treatment initiation according to the new criteria. Specifically, complete response required negative serum and urine immunofixation and normal FLC ratio, very good partial response was defined as a difference between involved (amyloidogenic) and uninvolved FLC (dFLC) <40 mg/L, and partial response required a decrease of dFLC >50%.[34] Cardiac response or progression required a decrease or increase in N-terminal natriuretic peptide type-B (NT-proBNP) >30% and >300 ng/L.[34,35] Baseline NT-proBNP had to be >650 ng/L to be evaluable.[34] Renal response required a >50% decrease in proteinuria in the absence of a ≥25% reduction in eGFR plus a ≥0.5 mg/dL increase in serum creatinine.[36] Toxicity was assessed monthly. Since the criteria of organ (other than heart) progression and hematologic progression have not been updated since 2005, and considering that in AL amyloidosis organ dysfunction (particularly kidney damage) can progress despite hematologic response, we calculated and analyzed time to next therapy[37] or death.

The statistical methods are reported in the *Online Supplementary Material*.

Results

A total of 454 patients were diagnosed at the Pavia Amyloidosis Research and Treatment Center between January 2004 and September 2009. Of them, three (1%) died before starting therapy, 22 (5%) had IgM clones and received specific therapy, 20 (4%) received ASCT, 116 (26%) had potentially reversible contraindications to ASCT and received stem cell-sparing treatment, and 34 (7%) had comorbidities precluding the administration of MDex. The remaining 259 patients (57%) were treated with MDex. Of them, 119 (46%) received full-dose therapy and 140 (54%) were treated with attenuated MDex. Their clinical characteristics are reported in Table 1. Patients receiving attenuated therapy were older and had lower eGFR and more advanced cardiac dysfunction. In particular, approximately 90% of patients treated with attenuated MDex had heart involvement, almost two thirds had stage III, and about 60% had New York Heart Association class III or IV heart failure.

Response to therapy

In an intent-to-treat analysis, 162 patients (62%) achieved hematologic response after cycle 3, which was a complete response in 54 subjects (21%), very good partial response in 63 (24%) and partial response in 45 (17%). The rate of hematologic response was significantly higher in patients receiving full-dose MDex both in the intent-to-treat analysis (76% *versus* 51%, P<0.001) and in a 3-month

Table 1. Patients' characteristics.

Variable	Full-dose MDex (N=119) N. (%) or median (range)	Attenuated MDex (N=140) N. (%) or median (range)	P
Gender, male	78 (66)	83 (59)	0.302
Age, years	64 (38-84)	69 (41-81)	<0.001
Age ≥70 years	26 (22)	66 (47)	<0.001
Heart involvement	67 (56)	122 (87)	<0.001
Standard staging I / II / III[1]	36 (30) / 68 (57) / 15 (13)	7 (5) / 49 (35) / 84 (60)	<0.001
Revised cTnI-based staging I/II/III/IV[2]	51 (43) / 39 (33) / 19 (16) / 10 (8)	16 (11) / 22 (16) / 46 (33) / 56 (40)	<0.001
NT-proBNP, ng/L	1051 (49-20791)	5524 (42-179300)	<0.001
NT-proBNP >1800 ng/L	41 (34)	111 (79)	<0.001
NT-proBNP >8500 ng/L	12 (10)	50 (36)	<0.001
cTnI, ng/mL	0.03 (0.0-0.85)	0.13 (0.01-8.24)	<0.001
cTnI >0.7 ng/mL	20 (17)	89 (64)	<0.001
NYHA class III or IV	31 (26)	80 (57)	<0.001
Kidney involvement	82 (70)	87 (62)	0.255
Proteinuria, g/24h	2.6 (0.1-22.2)	2.2 (0.1-20.0)	0.519
eGFR <30 mL/min/ 1.73 m^2	12 (10)	22 (16)	0.181
eGFR <60 mL/min/ 1.73 m^2	41 (34)	73 (52)	0.004
Liver involvement	15 (13)	27 (19)	0.146
PNS involvement	28 (24)	22 (16)	0.112
Organs involved	2 (1-5)	2 (1-5)	1.000
Light chain isotype, λ	95 (80)	115 (82)	0.636
Bone marrow plasma cell, %	10 (2-30)	10 (2-30)	0.443
dFLC, mg/L	143 (0-4822)	191 (1-6332)	0.069
dFLC >180 mg/L	47 (41)	76 (45)	0.017

cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; dFLC, difference between amyloidogenic (involved) and uninvolved circulating free light chains; NT-proBNP, N-terminal pro-natriuretic peptide type-B; NYHA, New York Heart Association; PNS, peripheral nervous system. [1]The standard staging system is based on NT-proBNP (cutoff 332 ng/L) and cTnI (cutoff 0.1 ng/mL). Stage I patients have both markers below the cutoff, stage II one marker, and stage III both markers above the cutoff. [2]The revised staging system is based on NT-proBNP (cutoff 1800 ng/L), cTnI (cutoff 0.07 ng/mL), and dFLC (cutoff 180 mg/L). Stage I, II, III, and IV patients have none, one, two or three markers above the cutoffs, respectively.

landmark analysis excluding the 25 subjects who died before evaluation of response (76% *versus* 62%, *P*=0.031). All early deaths occurred among subjects receiving attenuated treatment (see the section on survival). The higher hematologic response rate in the full-dose group was due to a higher proportion of complete responses (Table 2). A multivariable regression analysis showed that age <70 years (*P*=0.047), dFLC ≤180 mg/L (*P*=0.025), and treatment with full-dose dexamethasone (*P*=0.010) were independent predictors of complete response. After a median follow-up of 70 months (range, 17-95 months) following treatment discontinuation, complete response is maintained in 38 patients (70%). Overall, the median number of cycles of treatment given was six both in patients attaining complete response and in those reaching less than complete response.

By intent-to-treat analysis, organ responses were achieved in 43 patients (36%) who received full-dose MDex and in 30 (21%) of those treated with the attenuated schedule (*P*=0.009) after cycle 3. Organ responses were observed only in patients who attained hematologic response, and were more frequently associated with complete response than with very good partial response or partial response (68%, 22%, 10%, respectively; *P*<0.001). Cardiac and renal responses are reported in Table 2. By intent-to-treat analysis, there was a significantly higher rate of cardiac responses in subjects receiving full-dose treatment, but this was not confirmed in the landmark analysis. Improvement of organs other than the heart and the kidney was rare and observed only in the full-dose group. Two patients (13%) fulfilled the criteria for liver response, and two subjects (8%) obtained improvement of peripheral neuropathy. No baseline variable was found to be associated with cardiac response, which was only determined by hematologic response (*P*<0.001). Differently, renal response at 3 months was unlikely in patients whose eGFR at presentation was below 60 mL/min/1.73 m^2 (28% *versus* 10%, *P*=0.011). Baseline proteinuria did not influence renal response. Multiple regression analysis showed that eGFR ≥60 mL/min/1.73 m^2 (*P*=0.004) and hematologic response (*P*<0.001) were independent predictors of renal response. The patients with baseline eGFR <60 mL/min/1.73 m^2 were at increased risk of requiring dialysis within 2 years (40% *versus* 7%, *P*<0.001). When all patients who had at least a 50% decrease in proteinuria were considered responders, irrespective of changes in eGFR, there was still a higher rate of renal responses in subjects with eGFR ≥60 mL/min/1.73 m^2 (34% *versus* 13%, *P*=0.010). Since renal response can be delayed in AL amyloidosis, we analyzed renal response according to the current consensus criteria in patients surviving 1 year, and found that the response rates were 36% and 19% in patients with eGFR above and below 60 mL/min/1.73 m^2, respectively (*P*=0.046).

Leung *et al.* recently reported that a >75% decrease in proteinuria irrespective of creatinine changes is associated with a survival advantage.[38] In the present series, this was observed in 24 of 203 subjects (12%), 14 of whom received full-dose MDex. This pronounced reduction in proteinuria was associated with a trend for improved survival, although it did not reach statistical significance.

Treatment toxicity

A total of 47 patients (18%) experienced severe (grade 3 or 4) adverse events. The frequency of severe adverse events was not significantly different between the patients receiving full-dose treatment (16%) and those receiving attenuated treatment (20%) (*P*=0.401). The most common severe adverse event was fluid retention, observed in 22 subjects (8%), with comparable frequencies in the two groups despite dexamethasone dose reduction (9% *versus* 8%, *P*=0.690). Other rarer severe adverse events were neutropenia (11 patients, 4%), anemia (8 patients, 3%), infection (5 patients, 2%), deep venous thrombosis (2 patients, 1%), thrombocytopenia (1 patient, 0.5%), and liver toxicity attributed to melphalan (1 patient, 0.5%). One patient died of acute myeloid leukemia while in partial remission with a cardiac response 40 months after treatment discontinuation. He had received six cycles of MDex (total dose of melphalan: 384 mg). The median dose of melphalan in the whole cohort was 280 mg (range: 40-560 mg). The median number of cycles of treatment administered was five (range, 1-9); however, the patients treated with attenuated MDex received a significantly lower number of courses (median 4 *versus* 6, *P*<0.001). Treatment was discontinued before completion of cycle 3 in 29 subjects (11%), due to death in 25 patients (all treated with attenuated MDex), fluid retention in three (2 receiving full-dose dexamethasone), and liver toxicity in one (treated with the attenuated schedule). Twenty-eight (97%) of the patients who discontinued therapy were in stage III, and 21 (72%) had NT-proBNP >8500 ng/L.

Survival

Overall, 141 patients (54%) died. The median survival was 47 months and the median follow-up of living patients was 60 months. Patients receiving full-dose MDex survived longer than those treated with the attenuated schedule (89 *versus* 20 months, *P*<0.001, Figure 1A). The overall median time to second-line therapy or death

Table 2. Response to therapy.

	Intent-to-treat analysis			3-month landmark analysis		
	Full-dose (N=119) N (%)	Attenuated (N=140) N (%)	*P*	Full-dose (N=119) N (%)	Attenuated (N=115) N (%)	*P*
CR	37 (31)	17 (12)	<0.001	37 (31)	17 (15)	0.003
VGPR	35 (29)	28 (20)	0.078	35 (29)	28 (24)	0.383
PR	19 (16)	26 (19)	0.581	19 (16)	26 (23)	0.200
Cardiac	25/67 (37)	24/122 (20)	0.008	25/67 (37)	24/97 (25)	0.084
Renal	20/82 (24)	15/87 (17)	0.252	20/82 (24)	15/71 (21)	0.599

CR: complete response; PR: partial response; VGPR: very good partial response.

was 21 months. This was also longer in patients receiving full-dose treatment (median 30 *versus* 13 months, *P*<0.001, Figure 1B). Twenty-five patients died in the first 3 months after diagnosis, before being evaluable for response. All of them were treated with attenuated MDex and represented 18% of the patients in this group.

The baseline levels of the difference between involved and uninvolved free light chains (dFLC), NT-proBNP, and cardiac troponin I (cTnI) were found to be significant predictors of survival. The best prognostic cutoffs were dFLC >180 mg/L, NT-proBNP >1800 ng/L, and cTnI >0.07 ng/mL. Interestingly, the NT-proBNP and dFLC cutoffs were the same as those recently proposed by Kumar and co-workers in the revised Mayo Clinic staging system, which used cardiac troponin T instead of cTnI.[39] Combining these cutoffs, we were able to discriminate four groups with significantly different outcomes (Figure 2). The Cox univariable and multivariable analyses of survival based on variables observed at diagnosis is shown in Table 3. We generated a multivariable model including New York Heart Association class, and found that the use of high-dose dexamethasone was associated with an independent survival advantage. Recently, it has been shown that subjects with both NT-proBNP >8500 ng/L and systolic blood pressure <100 mmHg are at high risk of early death.[40] Overall, 62 patients had NT-proBNP >8500 ng/L (50 receiving attenuated MDex), and their median survival was 7 months. Only nine stage III patients with both NT-proBNP >8500 ng/L and systolic blood pressure <100 mmHg were included in the present study, and all of them died, with a median survival of 3.1 months (range, 1.9-79.0 months). They all received attenuated MDex.

In the 3-month landmark analysis, hematologic response to treatment significantly improved survival (Figure 3A), with best outcomes observed for those who obtained a complete response (93% 5-year survival) compared to those with a very good partial response (60%), partial response (37%) and no response (22%). Complete response had the greatest impact on time to second-line therapy or death, with only 21% of patients requiring further treatment at 5 years, compared with 67% of those with a very good partial response and 81% of those with a partial response (Figure 3B). Cardiac response and progression as assessed by changes in NT-proBNP significantly affected overall survival. The median survival of patients who attained NT-proBNP response was 82 months, compared to 48 months in patients with stable NT-proBNP, and 24 months in those in whom NT-proBNP progressed (*P*=0.001). Importantly, hematologic response was associated with better survival in each of the four risk stages (Figure 4). In a multivariable analysis including patients who survived at least 3 months, hematologic response (HR 0.24, *P*<0.001) and stage (HR 1.86, *P*<0.001) were independent prognostic factors.

Second-line therapy after mephalan and dexamethasone

Of the 72 patients who survived at least 3 months but did not respond to MDex, three refused further treatment and 24 (33%) died before second-line therapy could be initiated. Among the remaining 45 refractory patients, 23 received cyclophosphamide, thalidomide and dexamethasone (CTD), 19 received bortezomib plus dexamethasone (BDex), and three underwent ASCT with melphalan 140 mg/m^2. None of the transplanted patients responded. Of the 23 subjects treated with CTD, only three (13%)

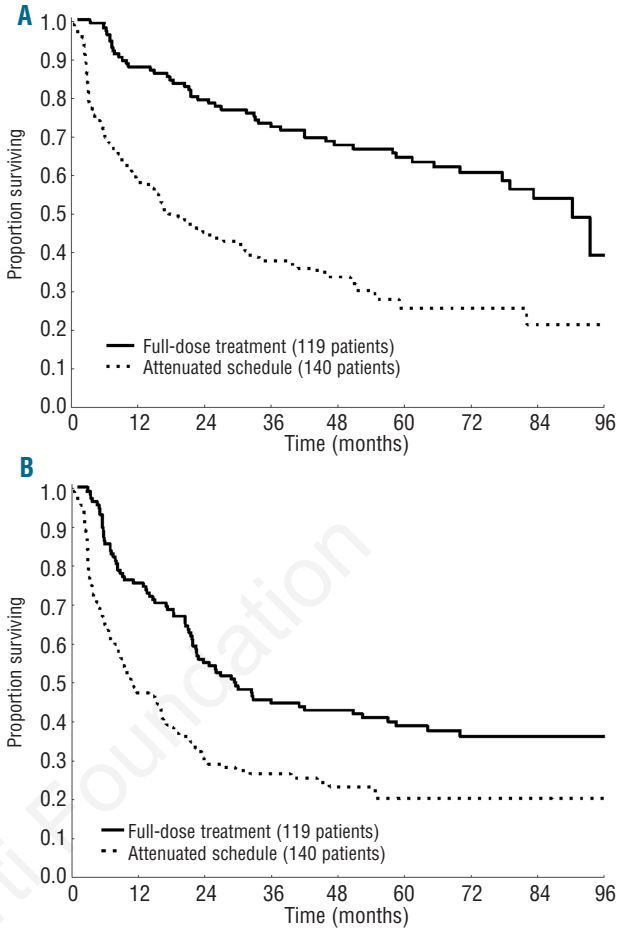

Figure 1. Survival and time to second-line therapy or death according to treatment intensity. (A) Overall survival (median 88 *vs.* 20 months, *P*<0.001). (B) Time to second-line therapy or death (median 30 *vs.* 13 months, *P*<0.001).

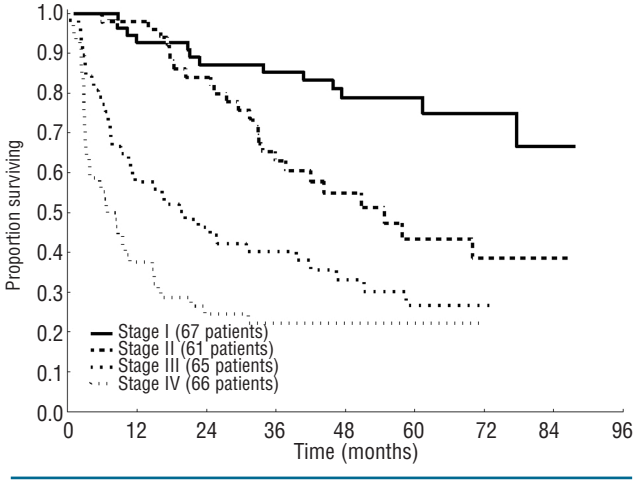

Figure 2. Survival according to the revised staging system. The revised staging system is based on NT-proBNP (cutoff 1800 ng/L), cTnI (cutoff 0.07 ng/mL), and dFLC (cutoff 180 mg/L). Stage I, II, III, and IV patients have none, one, two or three markers above the cutoffs, respectively. Stage I, median survival not reached. Stage II, median survival 52 months (*P*=0.003 compared to stage I). Stage III, median survival 19 months (*P*=0.003 compared to stage II). Stage IV, median survival 7 months (*P*=0.030 compared to stage III).

achieved a partial response. Conversely, 12 patients (63%) responded to BDex, with two complete responses.

Seventy-three patients who achieved at least partial response with MDex relapsed after a median time of 17 months, and were offered second-line treatment. Four were transplanted (melphalan 140 mg/m^2) achieving partial response in two cases and complete response in one. Ten patients received an additional three cycles of MDex, and nine responded, with two complete responses. Lenalidomide plus dexamethasone was used in six subjects, two of whom achieved a partial response. Twenty-five subjects were treated with CTD and seven of them (28%) responded, with four complete responses. Twenty-eight patients received BDex, achieving a hematologic response in 22 cases (79%), which was complete in seven subjects (25%). Response to second-line therapy translated into a significant survival benefit (median 13 months *versus* not reached, *P*=0.001).

Discussion

In patients who can withstand high-dose dexamethasone, MDex grants a high rate of hematologic response (76%), with complete remissions in 31% of cases. This results in an overall survival of 7.4 years, which compares favorably with that reported with ASCT (6.3 years) in the largest series published by the Boston University group.[41] However, in subjects with advanced cardiac dysfunction, who cannot receive high-dose dexamethasone, the outcome is poorer, with a 51% hematologic response rate and a median survival of only 20 months. This is in agreement with previous observations of an unsatisfactory performance of MDex in subjects with advanced cardiac amyloidosis.[5-7] This poor outcome is only partly explained by early deaths in high-risk patients. Indeed, the landmark analysis excluding patients who died before the evaluation of response still showed a significantly higher rate of complete response (31% *versus* 15%) in patients receiving full-dose treatment. This observation indicates that high doses of dexamethasone (40 mg for 4 consecutive days) are important to increase the likelihood of good quality responses.

Bortezomib combinations are currently being considered as alternative frontline regimens in patients with AL amyloidosis. Kastritis *et al.* reported an 81% hematologic response rate to bortezomib and dexamethasone in 18 previously untreated patients with AL amyloidosis, with the complete response rate being 47%.[42] The Mayo Clinic and United Kingdom groups reported on a total of 30 newly diagnosed patients treated with cyclophosphamide, bortezomib and dexamethasone, and observed a hematologic response rate of 90% (95% CI 73-98%), with 63% com-

Table 3. Baseline variables associated with survival (Cox analysis).

Variable	HR (95% CI)	*P*
Univariable analysis		
eGFR <60 mL/min/ 1.73 m^2	1.31 (0.94-1.82)	0.111
Age ≥70 years	1.69 (1.21-2.36)	0.002
dFLC >180 ng/L	2.03 (1.46-2.84)	<0.001
Attenuated dexamethasone	2.94 (2.08-4.17)	<0.001
cTnI >0.07 ng/mL	3.68 (2.54-5.34)	<0.001
NT-proBNP >1800 ng/L	3.41 (2.33-4.98)	<0.001
ln(NT-proBNP)	1.59 (1.42-1.78)	<0.001
Revised staging[1]	2.02 (1.69-2.41)	<0.001
NYHA class III or IV	2.39 (1.72-3.33)	<0.001
Multivariable model including NYHA class		
Age ≥70 years	1.42 (1.01-2.01)	0.046
NYHA class III or IV	2.22 (1.60-3.10)	<0.001
High-dose dexamethasone	0.39 (0.27-0.57)	<0.001

cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; dFLC, difference between amyloidogenic (involved) and uninvolved circulating free light chains; NT-proBNP, N-terminal pro-natriuretic peptide type-B; NYHA, New York Heart Association. [1]The revised staging system is based on NT-proBNP (cutoff 1800 ng/L), cTnI (cutoff 0.07 ng/mL), and dFLC (cutoff 180 mg/L). Stage I, II, III, and IV patients have none, one, two or three markers above the cutoffs, respectively. The cutoffs for dFLC, NT-proBNP and cTNI best predicting survival were generated by receiver operator characteristics (ROC) analyses based on death at 1 year. The areas under the ROC curves were 0.63, 0.80, and 0.79, respectively. The sensitivity and specificity were 61% and 62%, 88% and 64%, and 82% and 72%, for the dFLC, NT-proBNP and cTnI cutoffs, respectively.

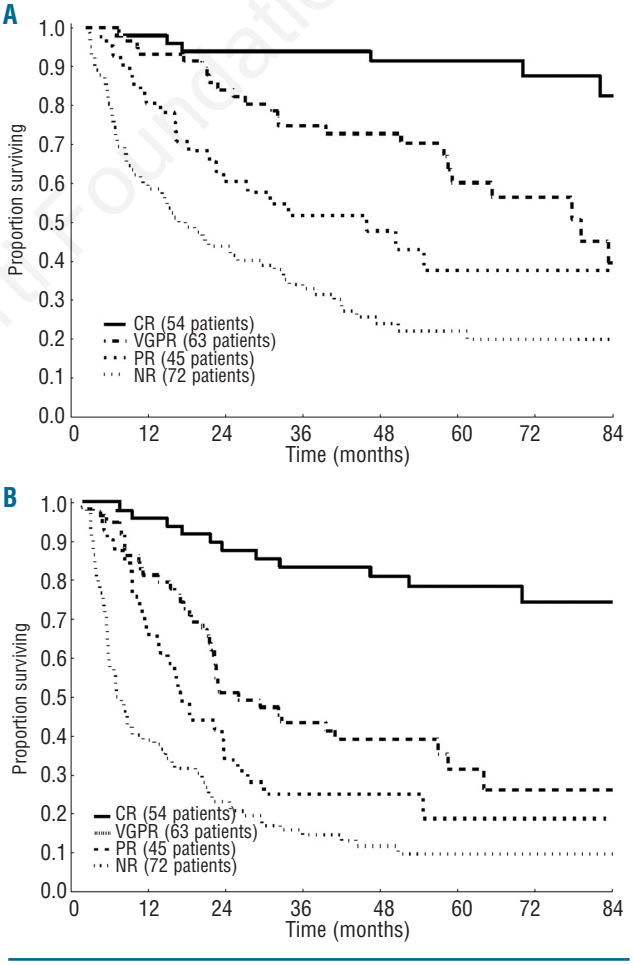

Figure 3. Survival according to response to treatment (3-month landmark analysis). (A) Overall survival according to hematologic response. Complete response (CR), median survival not reached. Very good partial response (VGPR), median 78 months (*P*=0.001 compared to CR). Partial response (PR), median 39 months (*P*=0.029 compared to VGPR). No response (NR), median 17 months (*P*=0.009 compared to PR). (B) Time to second-line therapy or death according to hematologic response. CR, median not reached. VGPR, median 25 months (*P*<0.001 compared to CR). PR, median 17 months (*P*=0.049 compared to VGPR). NR, median 7 months (*P*=0.006 compared to PR).

plete responses (95% CI 44-80%).[23,24] The overall response rate to full-dose MDex observed in the present study is comparable to that reported with bortezomib-based regimens, although the rate of complete responses is lower. Unfortunately, long-term follow-up of bortezomib combinations is still lacking. Achievement of complete response was associated with a higher rate of organ responses, with a significant prolongation of overall survival, and, even more strongly, with an improvement of time to second-line therapy. Remarkably the survival of patients achieving complete response was 93% at 5 years. However, effective second-line regimens, if available, could rescue a significant proportion of relapsed/refractory patients. While the efficacy of thalidomide combinations in subjects exposed to MDex seems unsatisfactory, bortezomib was the best rescue treatment, with 79% and 63% response rates in relapsed and refractory subjects, respectively.

In the present study, MDex proved well tolerated, with 18% of patients experiencing severe (grade 3 or 4) adverse events. However, since this was a retrospective study, toxicity might have been underestimated. There were no deaths in the first 3 months in patients treated with the full-dose schedule. In subjects receiving attenuated MDex, the rate of early deaths was 18%. However, dexamethasone dose reduction proved able to maintain the rate of severe adverse events, particularly fluid retention, in this group comparable to that observed in subjects exposed to full-dose treatment. There was only one case of secondary myelodysplasia. This low incidence confirms our previous reports,[1,2] and is probably due to the relatively low overall dosage of melphalan administered (median 280 mg). This was achieved by reducing the maximum number of cycles allowed to nine and by switching early to second-line regimens in patients with unsatisfactory responses, i.e. less than a very good partial response or partial response without organ response after three courses of MDex.

Baseline NT-proBNP, dFLC and cTnI were the main determinants of prognosis. Interestingly, the NT-proBNP and dFLC cutoffs best predicting survival in our patient population were identical to those recently identified by Kumar *et al.* in their revised staging system.[39] These findings in our patient population selected for treatment with MDex do, therefore, support the staging criteria proposed by Kumar and co-workers, and demonstrate that cTnI (cutoff 0.07 ng/mL) can be substituted for cTnT in the system. Exposure to high-dose dexamethasone was an additional prognostic factor, which was independent from

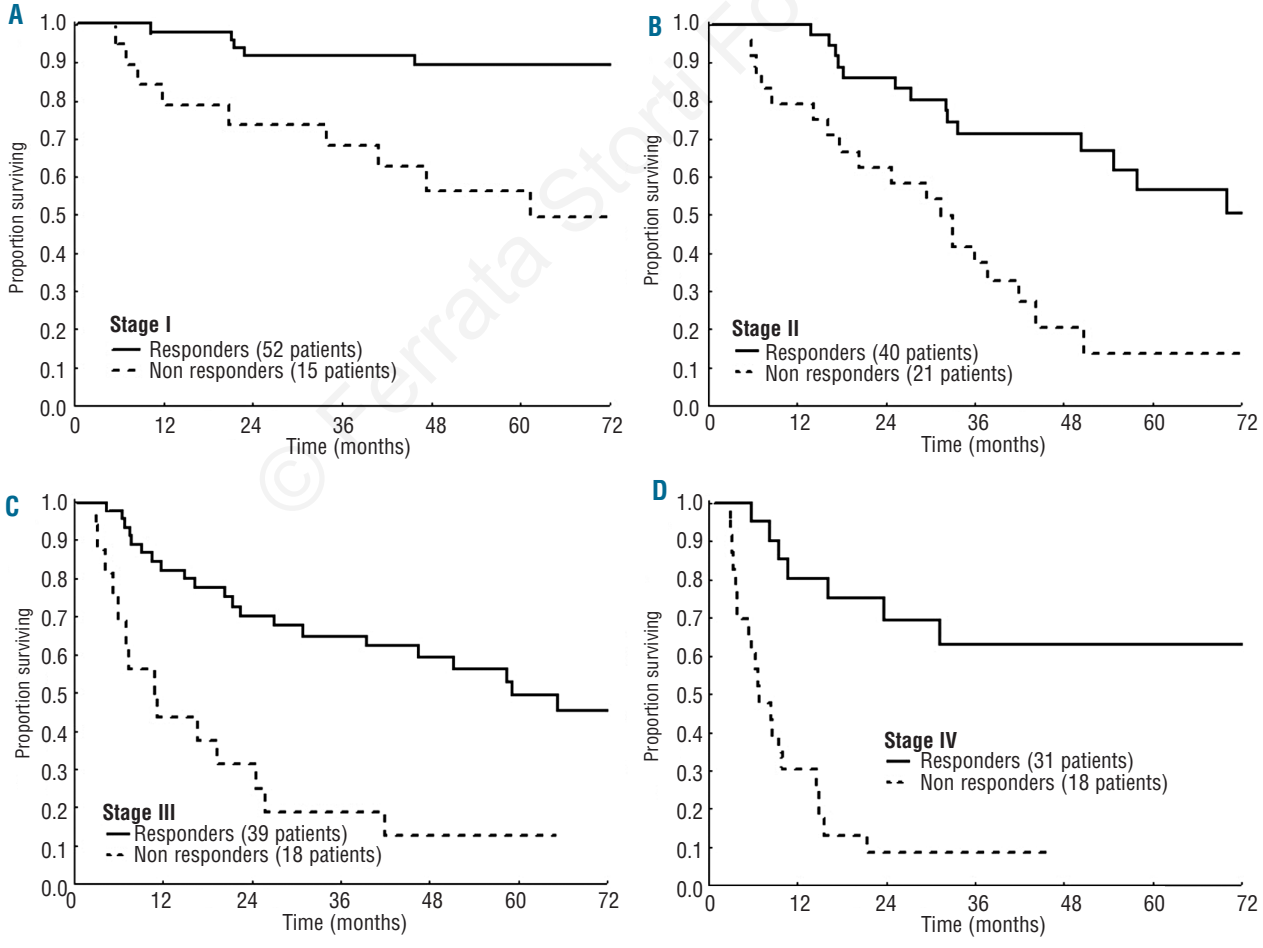

Figure 4. Survival according to hematologic response in the different risk stages. (A) Stage I. Median 60 months *vs.* not reached (*P*=0.003). (B) Stage II. Median 31 months *vs.* not reached (*P*=0.001). (C) Stage III. Median 11 *vs.* 59 months (*P*=0.001). (D) Stage IV. Median 7 *vs.* not reached (*P*=0.001).

parameters of disease severity at multivariable analysis, emphasizing the importance of full-dose therapy to maximize treatment efficacy. Hematologic and cardiac responses, assessed by the new international criteria, were also additional, independent determinants of survival. Importantly, hematologic response was able to significantly extend survival also in high-risk subjects, with 50-60% of responding stage III and stage IV patients surviving more than 5 years.

In summary, the present study in a large population of patients showed that MDex is very well tolerated and highly effective when high-dose dexamethasone can be used. With a response rate of 76%, a median survival of 7.4 years, no treatment-related deaths and severe adverse events in only 16% of cases, MDex is entitled to remain standard therapy for intermediate-risk patients with AL amyloidosis until randomized trials prove the superiority of different treatment approaches. In particular, since unsatisfactory responses to MDex can be effectively rescued with bortezomib, it will be important to elucidate whether the upfront combination of bortezomib with alkylating agents and dexamethasone confers benefit over the sequential use of bortezomib after MDex, at a reasonable cost in terms of toxicity. Differently, in subjects who are at high risk of early death (i.e. with NT-proBNP >8500 ng/L), in whom MDex performs less satisfactorily, it is reasonable to use drug combinations, with attenuated doses, including bortezomib to exploit the rapid activity of the proteasome inhibitor. In these fragile subjects drug synergism may compensate the need for dose reduction of bortezomib and dexamethasone.[43]

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Authorship and Disclosures

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