Long-term risk of myelodysplasia in melphalan-treated patients with immunoglobulin light-chain amyloidosis

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ABSTRACT

Survival of patients with plasma cell disorders has increased. However, the expanding use of melphalan in patients with longer survival suggests that myelodysplasia may become increasingly important. The objective of this study was to determine the risk of myelodysplasia after treatment with melphalan for patients with amyloidosis. We reviewed the long-term follow-up data (more than 12 years) from 101 patients with immunoglobulin light-chain amyloidosis. We identified 10 patients with myelodysplasia or acute nonlymphocytic leukemia that directly caused death for 8 and transfusion dependency for 2. Two of the 10 patients did not have development of myelodysplasia until 144 months after first exposure to alkylating agents. The actuarial risk of myelodysplasia development at ten years was 18%. As the survival of patients with plasma cell disorders improves, myelodysplasia may be a more common cause of morbidity and mortality for this group.

Key words: acute nonlymphocytic leukemia, amyloidosis, immunoglobulin light chain, melphalan, myelodysplasia.

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Introduction

For more than 30 years, the risk of alkylator-induced myelodysplasia has been well recognized in the treatment of hematologic malignancies.[1] Previously, melphalan was the only treatment available for patients with myeloma and amyloidosis, even though it was known to be a direct cause of myelodysplasia.[2,3] However, because the median survival was three years for patients with multiple myeloma and 18 months for those with amyloidosis, the number of patients at risk for this devastating, late complication was small.

Use of melphalan declined substantially with the advent of stem cell transplantation, which carries a low risk (approximately 2%) of clinical myelodysplasia.[4] Moreover, a shift in treatment in the late 1980s emphasized corticosteroid-based combinations such as dexamethasone, thalidomide-dexamethasone, and vincristine-doxorubicin-dexamethasone; all were effective and spared patients from exposure to alkylating agents.[5] Nevertheless, the use of melphalan for myeloma and amyloidosis began to increase. The combination of melphalan and high-dose dexamethasone was reported as an effective regimen for patients with immunoglobulin light-chain amyloidosis who were ineligible for stem cell transplantation,[6] and response rates were similar to those of stem cell transplantation. A 5-year update confirmed the results and showed that they were durable.[7] A subsequent phase 3 trial[8] suggested that outcomes of patients with amyloidosis treated with melphalan-dexamethasone were equivalent to those treated with high-dose melphalan therapy plus autologous stem cell transplantation. These results launched the increasing use of oral melphalan for the management of patients with amyloidosis.

Melphalan-prednisone-thalidomide treatment is increasingly considered as an option for elderly patients with multiple myeloma,[9] and similar results have been observed after using a combination of melphalan, prednisone, and bortezomib.[10] Thus, melphalan use will likely be more common in the management of patients with multiple myeloma, and complications of melphalan should be expected with greater frequency.

Because the development of myelodysplasia is a time-dependent phenomenon, long-term follow-up is required to ensure that all patient data are captured. In this report, we describe more than 12 years of follow-up data from a uniformly treated cohort of patients and detail the high incidence of myelodysplasia.

Design and Methods

All patients in this study have been described previously[11]; however, the earlier publication reported only the response to therapy and survival as an end point. All patients provided written, informed consent before study entry, and the

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original protocol and this current review were both independently approved by the Mayo Clinic Institutional Review Board. Amyloidosis was confirmed histologically, and all eligible patients had a clinically detectable amyloidosis syndrome such as cardiomyopathy, nephrotic range proteinuria, peripheral or autonomic neuropathy, unexplained hepatomegaly, or debilitating soft tissue involvement. All patients were previously untreated. At study entry, patients had a granulocyte count greater than 0.75×10^9/L and a platelet count greater than 50×10^9/L. Patients with overt multiple myeloma or secondary, familial, or localized amyloidosis were ineligible for the study.

For the patients assigned to the melphalan-prednisone treatment arm, 1.05 mg/kg of melphalan was administered orally with every 6-week cycle (dosage was divided over seven days). Prednisone was administered orally for the same seven days (dosage, 0.8 mg/kg). Patients in the second treatment arm of this study were treated with melphalan, carmustine, cyclophosphamide, vincristine, and prednisone. The melphalan dosage in this protocol was 8 mg/m^2, administered orally for four days. The carmustine dosage was 20 mg/m^2 on day 1, and the cyclophosphamide dosage (administered parenterally) was 400 mg/m^2 on day 1. The vincristine dosage was 14 mg/m^2 (administered intravenously) on day 1, and the prednisone dosage was 40 mg/m^2 (administered orally) for four days. Treatment was repeated every six weeks. For both study arms, the goal was 18 cycles of treatment unless serious complications of toxicity developed that warranted cessation of therapy. Dosages were modified during treatment for thrombocytopenia, neutropenia, and renal insufficiency. The total amount of administered melphalan was approximately 20% lower in the group randomized to receive vincristine, carmustine, melphalan, cyclophosphamide, and prednisone.

Development of myelodysplasia was previously defined as bone marrow morphology consistent with dysplasia.[12] Patients had a reduction of neutrophils, platelets, or hemoglobin that was compatible with the dysplastic changes of the marrow. Bone marrow biopsies were not performed routinely during this study; they were performed after cytopenia was recognized and only if clinically indicated.

All patients were prospectively entered into a database, and long-term, follow-up data have been gathered since the study was initiated in August 1991. No patients were subsequently excluded, and none were lost to follow-up. Comparisons of patients with and without development of myelodysplasia were performed using nonparametric statistics; we used 2x2 contingency tables for nominal variables (Fisher exact test) and Wilcoxon rank sum test for continuous variables. Actuarial assessment of time to development of myelodysplasia was performed using Kaplan-Meier methods. All *p* values were 2-sided.

Table 1. Patients' characteristics.

Parameter	*Patients with MDS (n=10)*	*Patients without MDS (n=91)*	*p value*
Male, N.	7	56	0.60
Treatment, N.			0.20
MP	7	45	
VBMCP	3	46	
Type of amyloidosis, N.			
Kidney	8	46	0.08
Heart	1	50	0.007
Liver	1	23	0.30
Nerve	3	8	0.04
Age, median (IQR), years	68 (61-75)	60 (52-67)	0.03
Albumin, median (IQR), g/dL	2.9 (1.5-3.2)	2.9 (2.1-3.5)	0.30
Creatinine, median (IQR), mg/dL	1.1 (0.9-2.7)	1.1 (0.9-1.5)	0.70
Alkaline phosphatase, median (IQR), mcg/dL	199 (140-266)	205 (143-434)	0.50
Urine protein (24-hr collection), median (IQR), g/dL	3.6 (1.0-6.6)	1.4 (0.3-7.5)	0.50
Interventricular septal thickness, median (IQR), mm	10 (9.5-12.5)	13 (11-15)	0.01
Marrow plasma cells, median (IQR), %	7 (5-13)	10 (5-16)	0.40
Survival, median (IQR), mo	55 (35-105)	22 (5-95)	–

IQR: interquartile range; MDS: myelodysplasia; MP: melphalan; VBMCP: vincristine-carmustine-melphalan-cyclophosphamide-prednisone.

Results and Discussion

At least one cycle of melphalan-based chemotherapy was administered to 101 patients. As of the publication of this report, 89 patients have died, and 12 are actively monitored. Of the 12 survivors, the minimum follow-up period was 12.5 years. Table 1 shows patient characteristics stratified by myelodysplasia development (10 patients had myelodysplasia, 91 did not).

As previously shown,[13] age was a risk factor for development of myelodysplasia in melphalan-exposed patients (median age difference, eight years). Patients with cardiac amyloidosis had a reduced incidence of myelodysplasia. This finding was unsurprising because myelodysplasia, a time-dependent variable, did not develop in any patient until 14 months after treatment, and 28 of the 51 patients with cardiac amyloidosis died within 14 months after treatment. Thus, the competing risk of death for patients with cardiac amyloidosis reduced the risk of myelodysplasia development. Furthermore, patients without myelodysplasia generally had greater interventricular septal thickness than patients with myelodysplasia; this finding was consistent with the group's higher mortality rate (due to cardiac complications), and the shortened survival thereby precluded myelodysplasia development. In contrast, patients with peripheral nerve amyloidosis have much longer survival than patients without peripheral nerve involvement[14] (in our cohort, 8 out of 11 with nerve amyloidosis survived longer than 14 months), and this group therefore had a disproportionately higher risk for development of late complications.

Table 2 provides specific characteristics of the 10 patients with myelodysplasia. Six of the 10 had classic abnormalities of chromosome 7. The one patient with a normal karyotype had classical morphological marrow features of myelodysplasia. All patients had neutropenia,

Table 2. Characteristics of patients with myelodysplasia.

Patient	Sex	Age, y	Time from melphalan exposure to diagnosis of MDS, mo.	Survival after MDS diagnosis, mo.	Absolute neutrophil count, x10^9/L	Metaphase cytogenetics	Cause of death	Platelet count, ×10^9/L
1	M	79	36	11	0.29	45,XY,-7,add(15)(p12)[5]/46, XY,del(7)(q22)[3]/46,XY[12]	MDS	121
2	M	52	76	14	0.35	46,XY[20]; subsequent marrow detected-7	ANLL; died of relapsing disease and graft-versus-host disease after allogeneic bone marrow transplantation	49
3	F	66	35	6	0.30	Not performed	ANLL	42
4	F	70	58	5	1.13	44,XX,-3,del(5)(q13q33),-7,-21,+mar[cp6]/46,XX[2]	MDS	16
5	F	66	144	>10[a]	0.90	46,XX,+1,der(1;7)(q10;p10)[14]/46,XX[7]	–	148
6	M	71	15	3	0.11	46,XY[20]	MDS and pneumonia	17
7	M	74	144	11	0.54	46,XY,del(20)(q11.2q13.3)[5]/92, idemx2[1]/92,XXYY[2]/46,XY[22]	ANLL	30
8	M	44	74	3	0.70	43-45,XY,del(1)(p22p32),dic(6;21)(q23;q22), -7,add(9)(q12),del(9)(q12),-11,add(14)(q12),-21, add(22)(p13),der(22)(7;22)(p11.2;p13)[cp14]/46, XY[2]	MDS	9
9	M	77	14	7	0.59	47,XY,+8[2]/46,XY[18]	MDS and dialysis	24
10	M	65	32	7	0.35	45,XY,del(5)(q11.2q33),-7[13]/45, idem,del(12)(p13)[2]/46,XY[5]	ANLL	69

ANLL: acute nonlymphocytic leukemia; MDS: myelodysplasia. [a]Patient was alive at the time of publication.

and all had a platelet count less than 0.15×10^9/L. The median time for disease development was 58 months, but we note that 2 patients did not show evidence of myelodysplasia until 144 months after their initial exposure to melphalan. The median survival after establishing the myelodysplasia diagnosis was 6.5 months. The overall survival of the 10 patients after study enrollment was 55 months, which was substantially greater than the survival of patients without myelodysplasia (22 months). However, these results were skewed because patients had to survive long enough for myelodysplasia to develop.

As noted in Table 2, myelodysplasia or acute nonlymphocytic leukemia was the direct cause of death in 6 patients. A seventh patient underwent allogeneic bone marrow transplantation (with full-intensity conditioning) and died of a transplantation-related complication. An eighth patient was receiving concurrent dialysis treatment, and the direct cause of death (dialysis *vs.* dysplasia) could not be determined. The one surviving patient is transfusion-dependent (hemoglobin, 9.9 g/dL; mean corpuscular volume, 112.5 fL; neutrophils, 0.9×10^9/L). Figure 1 shows the actuarial risk of myelodysplasia development: at 10 years, the risk was 18%, and at 12 years, the risk was 30%.

Twenty years ago, a distinct shift occurred in the management of patients with myeloma and amyloidosis from alkylating agents to dexamethasone-based regimens. However, a recent study of elderly patients with multiple myeloma reported no difference in the overall survival of those treated with melphalan and prednisone and of those treated with dexamethasone-based regimens.[15] These results indicated that dexamethasone need not be recommended routinely as first-line treatment for

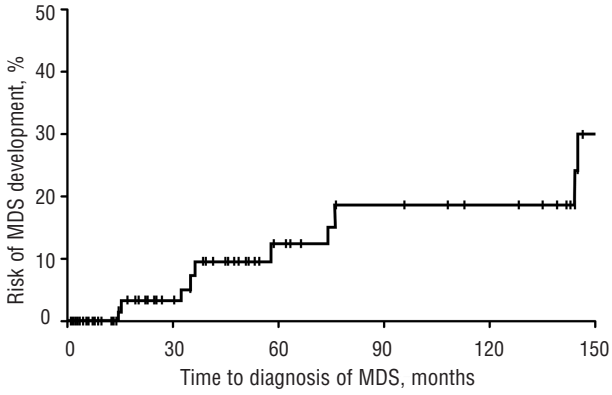

Figure 1. Actuarial risk of myelodysplasia in 110 patients with primary amyloidosis. Each tick mark represents a patient who died before myelodysplasia or acute nonlymphocytic leukemia developed.

elderly patients. Although the study had limitations (it pre-dated the introduction of novel agents for the treatment of myeloma and amyloidosis and did not include the recently introduced weekly dexamethasone schedule in the 4-arm study design), melphalan, in combination with novel agents, is becoming the standard treatment for patients with myeloma over 65 years of age.[9,16] Differences in treatment between patients in the study cohort and those of our current practice include a longer duration of chemotherapy for study patients (18 months) compared with exposures of 6-14 months for current melphalan-containing regimens. In our cohort, the patients with development of myelodysplasia consistently received more than 1,000 mg of melphalan. With current regimens, melphalan dosages should not exceed 600 mg; this may have the important effect of reducing the risk of myelodysplasia.

The median survival of patients with amyloidosis was previously thought to be about 18 months,[17] but this changed dramatically to about five years with the introduction of the melphalan-dexamethasone regimen for management[6] and to about 41 months with the use of orally administered cyclophosphamide, thalidomide, and dexamethasone.[18] With improved therapy, survival periods of ten years or longer will likely become common. With longer survival, increased exposure to melphalan may result in therapy-related acute nonlymphocytic leukemia and myelodysplasia.[19] When the survival of patients with myeloma and amyloidosis was short, late complications of melphalan were difficult to ascertain because the risk of death from myeloma was 10-fold greater than the risk of a treatment-related complication.[20] As therapies become more effective and patients live longer, the risks may change. Our study shows that the overall risk of myelodysplasia development was 10%, but the actuarial risk rose from 18% at ten years to 30% by 12 years.

Other studies may underestimate the risk of late myelodysplasia because many only report the response to therapy and relapse-free survival rate and lack prolonged follow-up data. Late risks cannot be estimated accurately by using reports with median follow-up periods of approximately five years. In our study cohort, a more accurate appraisal of the risk of alkylating agents can be made because we lost no patients to follow-up and had a minimum follow-up period of 12 years for the survivors.

Because of the low proliferative rate of plasma cells in primary amyloidosis, metaphase cytogenetic data are usually uninformative. Standard cytogenetic analysis was performed in 21 patients with primary amyloidosis, and adequate metaphase results were obtained in 20 (95%). Results were normal in 18. In one patient, the sole abnormality was absence of chromosome Y. In another patient who had previously been exposed to alkylator therapy, 46,XX,+der(1;7)(q10;p10),-7[10]/ 46,XX was found but likely was not reflective of the plasma cell clone.[21] When chromosome damage is identified after melphalan therapy, it localizes to myeloid but not plasma cells (as shown by fluorescence *in situ* hybridization and immunofluorescent cytoplasmic light-chain staining).[22] IgH translocations are usually observed, most commonly t(11;14)(q13;q32).[23] Patients with primary amyloidosis do not appear to have an intrinsic predisposition to development of myelodysplasia.

Stem cell transplantation remains an effective regimen, with a 1-2% treatment-related mortality rate in myeloma and a 10-15% rate in primary amyloidosis. The risk of clinical myelodysplasia is 2%.[4] For patients ineligible for transplantation, prolonged exposure to alkylating agents may result in an overall risk of 10% for myelodysplasia and an actuarial risk of 18%. Clearly, knowledge of these risks will not alter the management of patients with myeloma and amyloidosis, but clinicians should remember to discuss the possibility of treatment-related late risks with patients so that fully informed decisions can be made. Redevelopment of this previously recognized complication may occur in the future.

Authorship and Disclosures

MAG: conception and design, acquisition of data, analysis and interpretation of data; MQL, JAL, PRG, TEW, RAK: acquisition, analysis and interpretation of data. The authors reported no potential conflicts of interest.

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