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THE ASSOCIATION OF MELPHALAN AND HIGH-DOSE DEXAMETHASONE IS EFFECTIVE AND WELL TOLERATED IN PATIENTS WITH AL (PRIMARY) AMYLOIDOSIS INELIGIBLE FOR STEM CELL TRANSPLANTATION

Running head: Melphalan and dexamethasone in AL amyloidosis

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ABSTRACT

The most efficient therapeutic approach for immunoglobulin light chain amyloidosis (AL) is autologous stem cell transplantation (ASCT), however, the toxicity of ASCT limits its feasibility to a minority of patients. Patients ineligible for ASCT are usually treated with standard oral melphalan and prednisone, but the response rate to this regimen is unsatisfactory and time to response is long. High-dose dexamethasone provides a rapid response time in AL patients. We evaluated the combination of oral melphalan and high-dose dexamethasone (M-Dex) in 46 AL patients ineligible for ASCT. Thirty-one (67%) achieved a hematologic response and 15 (33%) a complete remission. In 22 of the responsive patients (48%) functional improvement of the organs involved was observed. Five patients (11%) experienced severe adverse events, 3 required hospitalization, no treatment-related deaths were observed. M-Dex represents a feasible and effective therapeutic option for patients with advanced AL who are ineligible for ASCT.

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INTRODUCTION

Immunoglobulin light chain amyloidosis (AL) is caused by a usually small bone marrow plasma cell clone, synthesizing monoclonal light chains that undergo conformational modifications and aggregate into amyloid fibrils (1). In the systemic disease, the fibrils form extracellular deposits in one or more vital organs, most frequently the kidney, heart, liver and peripheral and autonomic nervous system (2). The prognosis of patients with systemic AL is poor: the Mayo Clinic Group reported a median survival of 12-18 months (2, 3). The main prognostic determinant is amyloid heart involvement (2). At present, the most effective approach to treating AL is high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), aimed at annihilating the amyloidogenic plasma-cell clone. However, ASCT-related mortality (21% even at referral centers) and toxicity limit the feasibility of transplantation to a minority of patients (4, 5), although patients who can not undergo this procedure are those in greatest need of prompt care. Patients ineligible for ASCT are usually treated with standard oral melphalan and prednisone. Although this regimen has a very low toxicity, only 28% of patients achieve a response that, in 30% of them, is obtained after more than 1 year (3). Time to response is crucial in AL patients, particularly in those who present with advanced disease. A previous study from our group showed that high-dose dexamethasone (HD-Dex) provides a rapid response (median 4 months) with a 35% response rate in an unselected series of patients (6). We reasoned that combining HD-Dex with melphalan, both effective and well tolerated in patients with advanced AL, could synergize their therapeutic effect.

METHODS

Forty-six patients referred between December 1999 and October 2002 to the coordinating Center of the Italian Amyloidosis Study Group in Pavia with a histological diagnosis of amyloidosis and evidence of plasma cell dyscrasia who did not meet the eligibility criteria for ASCT were entered into the study. All patients gave oral informed consent according to the Institutional Review Board guidelines. Eligibility criteria for high-dose chemotherapy and ASCT were: ≤2 organs involved, absence of severe cardiac involvement, creatinine ≤2 mg/dL, age ≤65 years, and normal respiratory function tests (5).

All patients underwent a complete physical examination, high resolution serum and urine immunofixation electrophoresis (7), complete blood count, assessment of renal and liver function, echocardiography and 24 h electrocardiogram monitoring (Holter ECG). Complex ventricular arrhythmias are associated with an increased risk of sudden death in AL (8) and, in our preliminary experience with conventional high-dose dexamethasone, we observed a relevant proportion of treatment-related fatal arrhythmias (6). Therefore, patients in whom the Holter ECG detected couplets and/or ventricular tachycardia received prophylactic amiodarone (200 mg/day, 5 days/week) which was then continued indefinitely.

The patients were treated with melphalan 0.22 mg/Kg and dexamethasone 40 mg given orally on days 1-4 every 28 days. Prophylactic omeprazole (20 mg/day), ciprofloxacin (250 mg bid) and itraconazole (100 mg/day) were also prescribed on days 1-10.

Hematological response to treatment was defined as a ≥50% decrease in serum and urine monoclonal component (MC). Functional improvement of the organs involved was assessed according to the Mayo Clinic Group (3). Complete hematological remission was defined as the disappearance of serum and urine MC at high-resolution immunofixation maintained for at least three months. The response was evaluated every three months and established at the nadir of serum and urine monoclonal protein. Treatment was continued for up to 9 courses in patients who achieved the hematological response and discontinued if a complete hematological remission was obtained, if the monoclonal component increased and in the case of treatment-related toxicity.

A survival curve was plotted according to Kaplan-Meier and the difference in survival tested for significance with the log-rank test.

RESULTS AND DISCUSSION

Forty-six consecutive patients (33 males), were enrolled into the study. Their median age was 62 years (range: 34-79). A monoclonal protein was detected by high-resolution immunofixation in the serum and/or urine of all patients (32 λ, 9 κ, 5 biclonal).

High-dose chemotherapy and ASCT were contraindicated because of severe heart involvement in 32 patients (70%), involvement of more than 2 organs in 24 (52%), age >65 years in 17 (37%), creatinine >2 mg/dL in 2 patients (4%) and abnormal respiratory function tests in 1 patient (2%). Twenty-four patients (52%) were not eligible for ASCT for at least 2 criteria.

The heart was involved in 32 patients (70%), the kidney in 29 (63%), the peripheral nervous system in 11 (24%), the liver in 6 (13%), the soft tissues in 4 (9%) and the lung in 1 (2%). Sixteen patients (35%) had orthostatic hypotension. Thirty-five patients (76%) had more than 1 organ involved.

Median (range) urinary protein loss and serum creatinine in the whole group were 4 g/24h (0-24 g/24h) and 1 mg/dL (0.5-3.6 mg/dL), respectively. Twenty-seven patients had nephrotic range (≥3 g/24 h) proteinuria. The remaining two patients with renal amyloidosis had non-nephrotic proteinuria (1.6 and 2.7 g/24h) and one had renal failure (serum creatinine 2 mg/dL). Median (range) interventricular septum (IVS) thickness and ejection fraction were 14 mm (8-23 mm) and 50% (34-75%), respectively. In 15 patients (33%) the IVS thickness was >15 mm.

Patients were treated with a median of 4 courses (range: 1-9). Two patients died before completing the third cycle.

Thirty-one patients (67%) obtained a hematological response and 15 (33%) of these patients achieved complete hematological remission. The median time to response was 4.5 months (range: 2.3-10.1). Twenty-two patients (48%), in whom the MC decreased by at least 50%, also achieved significant functional improvement of involved organs (Table 1).

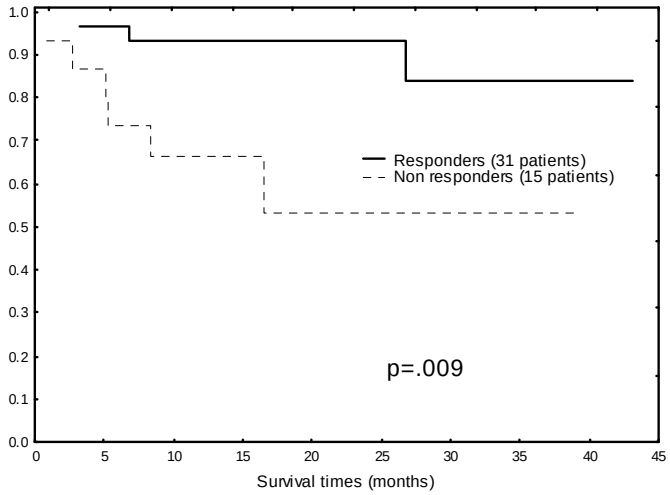
Table 1. Response to treatment

		Organ function improvement		**Total**
		Yes	**No**	
Hematological response	MC decrease >50%, MC present	9 (56%)	7 **(44%)**	16 (100%)
	Complete remission	13 (87%)	2 (13%)	15 (100%)
	No response	0 (0%)	15 (100%)	15 (100%)
	Total	22 (48%)	24 (52%)	46 (100%)

Fourteen of them had a ≥50% reduction of proteinuria, 6 had a ≥2 mm decrease in IVS thickness associated with resolution of heart failure, 1 patient, with lung involvement, had complete resolution of dyspnea and improvement of respiratory function tests (increase of vital capacity and forced expiratory volume), and 1 patient, with liver involvement, had normalization of alkaline phosphatase (from 451 to 178 U/L; reference <279 U/L). In 16 patients, organ and hematological responses were simultaneous, whereas in 6 cases organ function improved in a period ranging from 2.6 to 18.1 months (median: 4.6 months) after the hematological response. In 2 patients in complete remission, reported in Table 1, the organs involved (heart and kidney) did not improve and the patients are alive. In 14 of the 15 patients who achieved complete hematological remission, the response is maintained off therapy after a median follow-up of 16.4 months (range: 3-34). In one patient the monoclonal component reappeared after 29 months.

Five patients (11%) experienced severe (CTC grade ≥3) adverse events. Three patients had respiratory infections requiring admission to hospital. Two of them were the only patients who had not followed the antibiotic prophylaxis as prescribed. One patient, after the eighth cycle of M-Dex, developed reversible severe cytopenia which needed granulocyte colony-stimulating factor and platelet transfusional support. One patient, who had received two courses of M-Dex, developed a myelodysplastic syndrome.

The median follow-up of living patients is 20 months (range: 6-43) from starting therapy. Overall, nine patients (20%) died after a median follow-up of 5 months (1-27). Eight had severe heart involvement and died of heart failure (6 patients) and sudden death (2 patients), despite 2 of them having achieved a hematological response, although not complete remission. One patient died due to a pre-existing not amyloid-related obstructive lung disease, still in complete hematological remission, 27 months after therapy. Hematological response to therapy translated into a significant survival advantage (Figure 1).



These data show that 1) treatment with M-Dex is feasible and well tolerated in patients who are ineligible for ASCT due to advanced organ damage, 2) provides a high rate (67%) of durable responses in a short time (median: 4.5 months) with a positive impact on survival, and 3) produces significant organ function improvement in nearly half the patients.

Despite the fact that we selected patients with advanced disease, ineligible for ASCT, there was no treatment-related mortality and toxicity was low. M-Dex appeared to be a feasible option in this subset of patients and showed a good cost-effectiveness profile: during therapy, only three patients (6%), who developed respiratory infections, required admission to hospital. The response rate observed in this series (67%, 33% complete remission) compares favorably with that achievable in unselected patients with standard melphalan and prednisone (28%, complete remission not specified) (3) and also with the results obtained with HD-Dex (35% response rate, 9% complete remission) of our previous study (6). The short time to response (median: 4.5 months) is crucial in patients with advanced disease. One third of the patients achieved a durable complete hematological remission, a rare event in AL patients who cannot undergo transplantation. Despite advanced functional impairment, the reduction of the MC translated into improved function of the organs involved by the disease in 48% of patients and resulted into a significant survival benefit (Fig. 1). Most importantly, we observed resolution of heart failure in 6 of 32 cases. The observation of fatal heart failure despite reduction of the amyloidogenic protein >50% is not surprising considering the possible irreversible organ damage caused by the disease, and highlights the paramount importance of early diagnosis.

Patients who do not reach complete remission with M-Dex, but who obtain significant organ improvement might be re-evaluated for transplantation, although the exposure to the alkylating agent may jeopardize stem cell harvesting. In this respect, in patients who present with a potentially reversible contraindication for ASCT (i.e. isolated severe heart involvement), treatment with the modified HD-Dex regimen (6) may be considered, carefully weighing the lower response rate (67 vs. 35%) versus the preserved possibility of harvesting stem cells. Thalidomide is also an effective alternative, but unfortunately it is poorly tolerated by these fragile patients (9).

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Figure legend

Figure 1. **Patients' survival according to hematological response.**