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ORIGINAL ARTICLE

Treatment of patients with advanced cardiac AL amyloidosis with oral melphalan, dexamethasone, and thalidomide

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Abstract Patients with primary (AL) amyloidosis and heart failure have a very poor prognosis and cannot tolerate aggressive therapy, such as autologous stem cell transplantation and high-dose dexamethasone-based regimens. We prospectively treated 22 patients with advanced cardiac amyloidosis combining oral melphalan, thalidomide, and reduced intensity dexamethasone (MTD). Six patients died due to cardiac amyloidosis before completing cycle 3. Early death was associated with reduced ejection fraction. Eight patients achieved a hematological response and four achieved a durable improvement of cardiac dysfunction. Treatment with MTD is feasible in patients with advanced cardiac AL amyloidosis and effective in subjects with preserved systolic function.

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Introduction

In primary (AL) amyloidosis, not only is survival dependent on the presence of cardiac involvement but heart dysfunction also limits the feasibility of intensive and effective therapy [1]. The advent of dexamethasone-based regimens, particularly the combinations with melphalan (M-Dex) [2, 3] and with cyclophosphamide and thalidomide (CTD) [4], offered patients with advanced disease effective and less toxic alternatives to autologous stem cell transplantation (ASCT). However, patients with heart failure often cannot tolerate high-dose dexamethasone, because of fluid retention and ventricular arrhythmias [5]. Patients with isolated advanced cardiac involvement can undergo heart transplantation and subsequently receive aggressive chemotherapy with significant survival benefit [6]. However, in the majority of patients, severe amyloid cardiomyopathy is associated with multiorgan involvement. Moreover, patients with advanced cardiac dysfunction who present with heart failure and/or elevated serum concentration of N-terminal pronatriuretic peptide type B (NT-proBNP) and cardiac troponins have a short median survival (3.5 months) and need a rapidly effective treatment [7]. In multiple myeloma, the addition of thalidomide to melphalan and prednisone (MPT) improves the response rate and reduces the time to response to a median of 1.4 months [8]. This regimen proved more effective than ASCT in elderly multiple myeloma patients [9]. In AL amyloidosis, the combination of thalidomide with alkylating agents (cyclophosphamide) and dexamethasone (CTD) produces a high response rate (74%), with 50% of patients

obtaining at least a partial response after the first cycle [4]. In the present trial, we prospectively evaluated the safety and efficacy of a similar combination of melphalan, thalidomide, and low-dose dexamethasone (MTD) in patients with advanced cardiac AL amyloidosis.

Materials and methods

Twenty-two consecutive patients with AL amyloidosis with cardiac involvement and New York Heart Association (NYHA) class IV heart failure were included in the trial between November 2004 and April 2006. Three patients had attempted treatment with M-Dex but discontinued therapy due to fluid retention during the first course. The patients gave written informed consent and the study was approved by the Review Board of the "Fondazione Policlinico San Matteo".

Amyloidosis was characterized as AL type by immunoelectron microscopy on abdominal fat aspirates and hereditary amyloidoses were excluded by DNA analysis. Heart involvement was defined as mean left ventricular wall thickness >12 mm at echocardiography in the absence of other cardiac diseases, according to the International Society for Amyloidosis criteria [10]. All the patients underwent physical examination, high-resolution serum, and urine immunofixation electrophoresis, circulating free light-chain (FLC) measurement, complete blood count, assessment of renal and liver function, echocardiography, and 24-h electrocardiogram (Holter ECG). Holter ECG was repeated monthly, in order to identify thalidomide-induced bradycardia [11].

The patients received oral melphalan (0.22 mg/kg on days 1–4) and dexamethasone (20 mg on days 1–4), every 28 days, associated with continuous (100 mg/day) thalidomide. Prophylactic enoxaparine (4,000 IU/day), ciprofloxacin (250 mg bid on days 1–7), and omeprazole (20 mg/day on days 1–7) were administered. Amiodarone (200 mg/day) was also administered to patients who presented repetitive ventricular arrhythmias at Holter ECG.

Response was evaluated every three cycles. Response was defined according to the International Society for Amyloidosis criteria [10]. Hematologic response was defined as a >50% reduction of the concentration of the amyloidogenic FLC and complete remission (CR) as the disappearance of the monoclonal component at serum and urine immunofixation, normal FLC ratio, and bone marrow plasma cell of <5%. Cardiac response was defined as a ≥2-mm reduction of mean left ventricular wall thickness and/or a >20% increase in ejection fraction at echocardiography and/or improvement of two NYHA classes without increase in diuretic need. A >30% reduction of serum NT-proBNP concentration was considered a clinically significant improvement of cardiac dysfunction. This threshold was chosen considering the biological variability of NT-proBNP and because it was reported to translate into a survival advantage in patients with AL amyloidosis [12]. Treatment was discontinued in patients who achieved CR, in case of toxicity, or after completion of cycle 9.

Toxicity and adverse events were recorded according to the Common Terminology Criteria for Adverse Events version 3.0. A response rate of 35% was considered of interest, and 15% was assumed as the minimal clinically significant response rate. To test the hypothesis that the response rate was at most 15% with a significance level of 0.05, 22 patients were to be enrolled in the trial. A survival curve was plotted according to Kaplan–Meier.

Results

Twenty-two patients were enrolled in this prospective trial. The main clinical features are reported in Table 1. None of

Table 1 Characteristics of 22 patients with AL amyloidosis and advanced cardiac involvement treated with MTD

Patients' characteristics	*N* (%)	Median (range)
Gender (male)	14 (64)	
Age (years)		64 (48–74)
Kidney involvement	15 (68)	
Liver involvement	6 (27)	
Gastrointestinal involvement	1 (4)	
Number of organs involved in addition to heart		1 (1–3)
Postural hypotension	7 (32)	
mLVW (mm, upper reference limit 12 mm)		16 (13–21)
Ejection fraction (%, upper reference limit 55%)		55 (22–64)
Ejection fraction ≤55%	7 (32)	
NT-proBNP (ng/L, upper reference limit 334 ng/L)		11282 (1242–49680)
cTnI (ng/mL, upper reference limit 0.06 ng/mL)		0.13 (0.03–0.78)
cTnI >0.1 ng/mL	16 (73)	
Receiving amiodarone for repetitive ventricular arrhythmia at Holter ECG	4 (18%)	
Proteinuria (g/24 h)		0.6 (0.2–16.2)
Serum creatinine (μmol/L, upper reference limit 106.1 μmol/L)		127.3 (52.2–190.1)
Serum creatinine > 106.1 μmol/L	14 (64)	
Time from symptoms onset to diagnosis (months)		10 (1–59)

mLVW Mean left ventricular wall thickness, *NT-proBNP* N-terminal pronatriuretic peptide type B, *cTnI* cardiac troponin I

the subjects was a candidate for heart transplantation due to multiorgan involvement.

Eight patients (36%) obtained a hematological response and one of them achieved CR. In four patients (18%) at the time of hematologic response, a reduction of NT-proBNP >30% of the baseline value was also observed (median 54%, range 40–62%). In one of these patients, a 2-mm reduction in mean left ventricular wall thickness was also observed. Hematologic response was reached after three cycles in all but one patient, in whom the FLC concentration was 65% of that observed at presentation after cycle 3 and 29% after cycle 6. There was no significant difference in variables measured at enrolment between patients who obtained a cardiac response and the other patients who completed three cycles.

Six patients (27%) died due to cardiac amyloidosis before completing cycle 3 (four during cycle 1 and two during cycle 2). Of the remaining patients, six received three cycles of MTD, four and five courses were administered to one patient each, five patients received six cycles, and three patients completed nine cycles. Four of the patients who died before cycle 3 (67%) and three of the 16 patients who completed cycle 3 (19%) had an ejection fraction <55% (p=0.03), whereas there was no significant difference in the remaining variables. Hematological and organ response rates in patients completing cycle 3 were 50% and 25%, respectively.

Six patients (27%) experienced severe (grade ≥3), though nonfatal toxicity: fluid retention in two cases and renal failure, bradycardia, sepsis, and arterial embolism in one patient each. Thalidomide was discontinued in the four patients who presented adverse events other than fluid retention. No other patient required thalidomide discontinuation or dose reduction.

Eighteen patients (82%), four who achieved a hematological response and all nonresponders, died. Median survival was 5.3 months (Fig. 1). Causes of death were heart failure in 16 patients and sudden death in two. Only the four patients in whom NT-proBNP decreased survive, after a median follow-up of 28.3 months (range, 24.2–36.1 months).

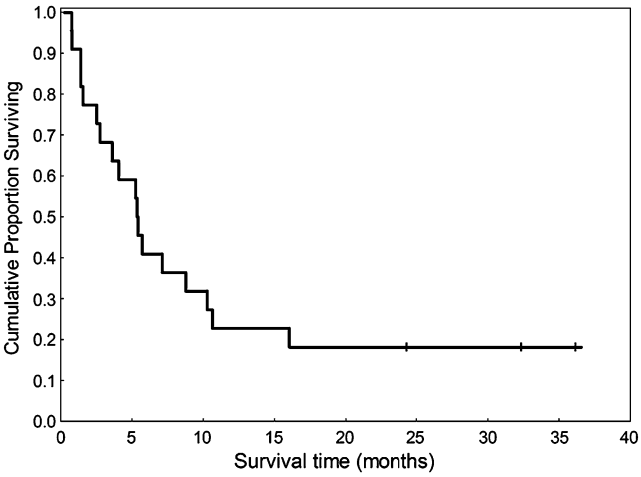

Fig. 1 Survival of 22 patients with advanced cardiac AL amyloidosis treated with MTD (median 5.3 months)

Discussion

Heart involvement is the most severe clinical manifestation of AL amyloidosis, accounting for more than 75% of overall deaths, and of nearly all of the 25% of deaths occurring in the first 9 months in our patient population. We have previously reported that the suppression of the synthesis of the amyloidogenic light chain translates into rapid reduction of NT-proBNP with survival benefit in the majority of patients [12]. The dramatic downhill course of patients with amyloid cardiomyopathy indicates that rapidly acting chemotherapy regimens are required to improve survival. The addition of thalidomide to alkylating agents, such as in the MPT regimen in multiple myeloma [8, 9] and in the CTD regimen in AL amyloidosis [4], accelerates the time to response, with half of the patients responding within 1.4 months from starting MPT and after the first CTD cycle, respectively. Also in our study with MTD, the responses were rapid, 90% of them being achieved after the first three courses.

The patients with severe heart failure are usually excluded from clinical studies on new therapies in AL amyloidosis and little is known on treatment outcome in these disadvantaged subjects. The present is the first trial specifically addressing treatment of patients with advanced heart failure. Response to MTD induced a durable improvement of cardiac dysfunction only in one fifth of cases. These patients survived longer than 2 years. However, nearly 30% of patients, particularly those who present with reduced ejection fraction at echocardiography, do not survive long enough to have a chance to respond. In these patients, heart transplantation, when indicated, represents at present the only viable alternative. In subjects with severe heart involvement but preserved ejection fraction, trials on rapidly acting regimens, such as the present one and possibly those containing bortezomib, seem warranted.

Approximately 20% of the patients discontinued thalidomide due to adverse reactions. In the present study, we adopted a lower dose (100 mg/day) than in our previous trial (escalation from 100 to 400 mg/day) [11]. It is possible that starting with an even lower thalidomide dose (e.g., 50 mg/day), like in attenuated CTD [4], might improve tolerability.

In 45% of cases, the diagnosis of amyloidosis was made 1 year or more after the onset of cardiac symptoms. Most likely, an earlier diagnosis would have widened the therapeu-

tic window, allowing patients to benefit from treatment. Thus, increasing the awareness on amyloidosis remains an important goal to be pursued in order to improve the patient care.

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