Cyclophosphamide + Thalidomide + Dexamethasone Versus Melphalan + Dexamethasone for the Treatment of Amyloid Light-chain Amyloidosis With Kidney Involvement: A Retrospective Study in Chinese Patients

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ABSTRACT

Purpose: At present, a diverse array of treatment regimens are available for systemic amyloid light-chain (AL) amyloidosis. Both cyclophosphamide + thalidomide + dexamethasone (CTD) and melphalan + dexamethasone (MD) regimens have been recommended as first-line therapies, but no detailed comparative studies of the two have been performed. This study is the first to compare the efficacy and tolerability of the CTD and MD regimens in the treatment of AL amyloidosis.

Methods: We retrospectively reviewed data from consecutive patients with AL amyloidosis who were treated with MD or CTD as the initial regimen between June 2012 and January 2018.

Findings: In the final analysis, 38 patients received CTD, and 30 received MD. There were no significant differences in baseline characteristics, including age, sex, renal function, involved organs, level of free light chains, and Mayo Clinic amyloidosis prognostic staging. The overall hematologic response rates in the CTD and MD groups were 69.0% versus 68.0%, respectively ($P = 0.94$), including a complete response in 27.6% versus 8.0% ($P = 0.14$). Neither group reached the estimated median overall survival, and the difference between the 2 groups was not significant ($P = 0.17$). The median progression-free survival times were 36 versus 14 months ($P = 0.24$) in the CTD and MD groups, respectively. The CTD group achieved a numerically but not statistically higher prevalence of kidney response (52.9% vs 37.0%; $P = 0.22$). The most common adverse events in the 2 treatment groups were fatigue (48.5% vs 21.7%; $P = 0.04$) and constipation, anemia, nausea/vomiting, neutropenia, and syncope (all, P = NS). Deaths occurred in 6 patients in the CTD group and 9 patients in the MD group; none were considered by the investigators as related to the study treatments. There were no other serious adverse events observed in our study.

Implications: The CTD regimen may not be inferior to standard oral MD in terms of overall hematologic response and overall survival. Although this study was of retrospective and negative-control design with some additional limitations, it may provide a therapeutic option for use in developing countries where patients cannot afford bortezomib or melphalan. (*Clin Ther*. 2019;41:1186–1198) © 2018 Published by Elsevier Inc.

Key words: amyloidosis, cyclophosphamide, immunoglobulin light chain, melphalan, thalidomide.

INTRODUCTION

Amyloid light-chain (AL) amyloidosis is a low–tumor-burden disorder characterized by deposition of misfolded monoclonal immunoglobulin light chains, resulting in serious systemic organ damage. AL amyloidosis is the most common type of the systemic amyloidosis, with an estimated incidence of 3–10 cases per million person-years in Western countries.[1,2] In patients in China, with the current economic development and aging population, AL

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amyloidosis is associated with increasing morbidity and a high risk for mortality, in addition to higher rates of renal involvement, compared with that in Western patients.[3] The prognosis of patients with primary systemic amyloidosis is poor, with one study reporting a median survival time of only 13.2 months in the absence of effective therapeutic intervention.[4] The consequences of AL amyloidosis have led to a serious economic burden in both patients and society.[5]

In the wake of the development of novel regimens, outcomes in patients with AL amyloidosis have largely improved in recent years.[6] Patients receiving high-dose chemotherapy and autologous stem-cell transplantation (ASCT) have been reported to have much greater response rates and lower treatment-related mortality.[7] Furthermore, these treatments have been recommended by the Mayo Clinic as the standard therapeutic regimen.[8] However, this treatment regimen is limited by rigorous criteria for treatment candidacy, resulting in a candidacy rate of only 20%.[9]

While initially used to treat multiple myeloma,[10] the combination of cyclophosphamide + thalidomide + dexamethasone (CTD) has been reported to be efficacious and well-tolerated in the treatment of AL amyloidosis in a prospective, observational study that concluded that CTD should be recommended as a first-line therapy because of its potential benefit.[8] In that study, a median overall survival (OS) of 41 months and a hematologic response rate of 74%, including 21% complete responses, were reported, with a median follow-up of 22 months.[11] The value of melphalan + dexamethasone (MD) in the treatment of AL amyloidosis has also been validated in a series of studies,[12–15] including a randomized controlled trial[15] in 100 selected patients randomized to receive either ASCT followed by high-dose melphalan or oral MD. Based on the intent-to-treat analysis, the estimated median OS in the MD group was 56.9 months, and MD was found to be noninferior to high-dose melphalan + ASCT.

However, considering the varying baseline characteristics of patients between the different centers, it is not advisable to compare the above-mentioned therapeutic outcomes. In addition, there have been no prospective or even retrospective studies comparing the 2 regimens. We therefore conducted a retrospective study to compare the efficacy and tolerability of the CTD and MD regimens in our center to provide evidence on treatment regimens in patients with AL amyloidosis.

MATERIALS AND METHODS

Patients

Data from patients who had been diagnosed with systemic AL amyloidosis with kidney involvement between June 2012 and January 2018 at the Department of Nephrology, Xijing Hospital (Xi'an, China), were retrospectively investigated. The histologic diagnostic criteria were Congo red–positive fibril deposition on biopsy and nonbranching fibrils 7.5 to 10 nm in diameter on electron microscopy. Immunohistochemistry staining confirmed single κ or λ light-chain positivity. Immunofixation electrophoresis of blood and serum free light chains (FLCs) also provided evidence of a monoclonal protein. Patients treated with MD or CTD as an initial formal regimen in our center were enrolled in our study, irrespective of whether they had previously received informal therapy or no intervention. Patients who had been treated with other regimens, had been followed up for <12 weeks (except for reaching an end point within 12 weeks), and who had been diagnosed with multiple myeloma according to the updated criteria enacted by the International Myeloma Working Group[16] were excluded from the final analysis.

The study protocol was approved by the Committee of Medical Ethics at Xijing Hospital, and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was also obtained.

Treatments

The CTD regimen consisted of an injection of cyclophosphamide 500 mg on days 1, 8, and 15; oral thalidomide at a starting dose of 50 mg/d and increased to 200 mg/d after 4 weeks if tolerated; and oral dexamethasone 20 mg on days 1–4 and days 15–18, of each 28-day cycle.

In the MD group, 0.17 to 0.20 mg/kg of melphalan and 40 mg of dexamethasone were given orally on days 1–4 of each 28-day cycle. If tolerated, the melphalan dose could be increased to 0.225 mg/kg.

The treatment cycles were continued until patients reached the point at which they achieved very good partial hematologic response (VGPR) or organ response. Treatment was discontinued in the absence of a hematologic response (no response; NR) or if a

serious adverse event occurred. In the CTD regimen group, additional thalidomide monotherapy (100 mg/d) was given as maintenance therapy to reduce the risk for relapse after a complete response (CR) was achieved.

Follow-up and Outcomes Evaluation

All patients were followed up in an outpatient clinic that specialized in the management of amyloidosis. Disease risk stratification and organ involvement were characterized using the Mayo Clinic Staging System 2012[17] (*Mayo staging*) and the National Amyloidosis Centre guideline,[18] respectively. Hematologic response was assessed according to the criteria of the International Society of Amyloidosis,[19] as follows: CR (normalization of the FLC ratio and negative serum and urine immunofixation), VGPR (a reduction in the difference between involved and uninvolved FLC [dFLC] to 40 mg/L), partial response (PR; a decrease in dFLC of >50%), and NR (a decrease in dFLC of <50%). Organ response was based on the First Roundtable on Clinical Research in AL Amyloidosis.[20] Notably, renal staging and renal response were defined using the criteria from a more recently published article.[21] Patients who died within 1 cycle were classified as NR. Response was evaluated every 3 treatment cycles.

OS was calculated from treatment initiation until death from any cause or the last follow-up. Progression-free survival (PFS) was measured from treatment initiation until disease progression, death, or last follow-up. The change in 24-hour urinary protein was defined as the difference between the measurements taken before treatment initiation and at the end of treatment.

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 4.0.[22] We assessed toxicity monthly and discontinued the chemotherapy when necessary.

Statistical Analysis

All statistical analyses were performed using SPSS software package version 24.0 (IBM, Armonk, New York). Survival was measured by the Kaplan-Meier method and compared by log-rank test. Continuous variables are described by mean (SD) or median (interquartile range) and compared using the *t* test or the Mann-Whitney *U* test. For categorical variables, frequencies are used to describe the results, and the χ^2 test or the Fisher exact test was applied for comparing them as appropriate. A multivariate analysis was performed by Cox regression and expressed by hazard ratios (HRs) and 95% CIs. In all analyses, 2-sided *P* values of <0.05 were considered statistically significant.

RESULTS

A total of 80 patients who received CTD or MD as a first-line regimen in our department between June 2012 and January 2018 were identified. Of these 80 patients, 12 who were followed up for <12 weeks were excluded. In the final analysis, the cohort was composed of 68 patients with systemic AL amyloidosis (CTD: 38 patients, median follow-up, 19 [6−33] months; MD: 30 patients, median follow-up, 13 [7−24] months). Renal involvement was confirmed by renal biopsy in 66 patients. One patient who was ineligible for renal biopsy underwent a subcutaneous-fat biopsy, and 1 patient underwent a liver biopsy. The median number of treatment cycles in the CTD and MD arms did not differ significantly (8.5 vs 6, respectively; $P = 0.13$). In 4 patients in the MD group, the regimen was switched due to a lack of hematologic or organ response. Of these patients, 2 received CTD as the alternative regimen after 4 and 20 cycles. The other 2 patients received bortezomib + dexamethasone after 3 and 17 cycles. In the CTD group, 1 patient was switched to the MD regimen after 4 cycles, and 2 patients were discontinued from therapy for lack of response. During the follow-up period, 4 patients (2 in each group) progressed to a need for dialysis, with times from diagnosis to dialysis of 2, 13, 14, and 45 months.

Baseline Characteristics

The baseline characteristics of the patients in the 2 groups at the commencement of the intervention are listed in Table I. In the entire cohort, 44 patients had cardiac involvement, and 9 patients had liver involvement. In addition to involvement of vital viscera listed in Table I, there were 3 patients with tongue involvement, 2 patients with skin involvement, and 1 patient with peripheral neuropathy. There were no significant differences in baseline characteristics between the 2 groups, including organ involvement, Mayo staging, and renal staging. However, patients who received the MD regimen had numerically but not statistically

higher levels of dFLC and cardiac biomarkers (N-terminal brain natriuretic peptide, brain natriuretic peptide, and troponin T).

Hematologic and Organ Responses

The hematologic and organ response rates in each group are described in Table II. In those who were switched between therapeutic regimens, responses were evaluated before switching. Among the 68 patients, hematologic response was assessed in 54 patients before April 1, 2018. There was no significant difference in overall hematologic response between the CTD and MD groups (69.0% vs 68.0%, respectively; $P = 0.94$). The CTD group had a

Table I. Patients' demographic and clinical characteristics at the commencement of chemotherapy.

Variable	CTD Group (n = 38)	MD Group (n = 30)	*P*
Age			
Mean (SD), y	56 (11)	59 (7)	0.14
≥65 y, no. (%)	9 (23.7)	6 (20.0)	0.72
Male, no. (%)	19 (50.0)	15 (50.0)	1.00
Time to diagnosis, median (range), mo	6 (3–12)	6 (4–18)	0.38
Blood pressure			
Supine SBP, mean (SD), mm Hg	114 (21)	113 (18)	0.78
Supine DBP, mean (SD), mm Hg	71 (11)	72 (12)	0.81
Hypotension, no. (%)*	10 (26.3)	7 (23.3)	0.78
Biochemistry			
Hb, mean (SD), g/L	129 (25)	123 (20)	0.33
Alb, mean (SD), g/dL	2.4 (0.7)	2.7 (0.8)	0.19
λ Subtype, no. (%)	26 (68.4)	23 (76.7)	0.45
dFLC, median (range), mg/L	42 (20–83)	92 (22–120)	0.17
NT-proBNP, median (range), ng/L	505 (198–2252)	1726 (379–5002)	0.07
BNP, median (range), ng/L	113 (56–352)	199 (106–623)	0.06
TnT, median (range), μg/L	0.020 (0.010–0.059)	0.039 (0.018–0.085)	0.12
Scr, mean (SD), μmol/L†	94 (35)	95 (61)	0.94
eGFR, mean (SD), mL/min/1.73 m^2	74 (21)	78 (24)	0.52
ALP, median (range), IU/L	80 (65–105)	85 (64–110)	0.76
Urinalysis			
24-h urinary protein, median (range), g	2.924 (1.840–4.032)	2.903 (1.313–4.549)	0.81
Proteinuria,‡ no. (%)	17 (45.9)§	15 (50.0)	0.74
Cardiac characteristics, mean (SD)			
IVS, cm	11.2 (2.2)	12.3 (2.6)	0.09
EF, %	60 (5)	58 (5)	0.13
Involved organ, no. (%)			
Kidney	38 (100)	30 (100)	NA
Heart	22 (62.9)‖	22 (75.9)¶	0.26
Liver	5 (13.2)	4 (13.3)	1.00
≥2 Organs involved	27 (71.1)	25 (83.3)	0.24
Renal impairment stage,# no. (%)			
I	30 (78.9)	21 (70.0)	0.40
II	8 (21.1)	9 (30.0)	0.40
III	0	0	NA

(*continued on next page*)

Table I. (*Continued*)

Variable	CTD Group (n = 38)	MD Group (n = 30)	*P*
Mayo stage,** no. (%)			
I	15 (45.5)	9 (31.0)	0.25
II	7 (21.2)	7 (24.1)	0.78
III	11 (33.3)	12 (41.4)	0.51
IV	0	1 (3.4)	0.47

Alb = albumin; ALP = alkaline phosphatase; BNP = brain natriuretic peptide; CKD = chronic kidney disease; DBP = diastolic blood pressure; EF = ejection fraction; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; IVS = interventricular septal thickness; NT-proBNP = N-terminal brain natriuretic peptide; SBP = systolic blood pressure; Scr = serum creatinine; TnT = troponin T.

* SBP of <100 mm Hg.

† 1 mg/dL = 88.41 μmol/L.

‡ Twenty-four-hour urinary protein excretion of >3 g.

§ n = 37.

‖ n = 35.

¶ n = 29.

Stage I, eGFR >50 mL/min and 24-hour urinary protein excretion of <5 g; stage II, eGFR <50 mL/min or urinary protein excretion of >5 g; stage III, eGFR <50 mL/min and urinary protein excretion of >5 g.[21].

** Mayo Clinic amyloidosis prognostic staging system[17]: a score of 1 is assigned for each of 3 prognostic variables (cardiac TnT ≥0.025 ng/mL, NT-ProBNP ≥1800 pg/mL, and difference in free light chains of ≥18 mg/dL); total scores of 0, 1, 2, and 3 are defined as stages I, II, III, and IV, respectively.

Table II. Hematologic and organ response.

Variable	CTD Group (n = 38)	MD Group (n = 30)	*P*
Hematologic response	(n = 29)	(n = 25)	
Any response	20 (69.0)	17 (68.0)	0.94
CR	8 (27.6)	2 (8.0)	0.14
VGPR	11 (37.9)	12 (48.0)	0.46
PR	1 (3.4)	3 (12.0)	0.50
NR	9 (31.0)	8 (32.0)	0.94
Organ response			
Kidney	18 (52.9) (n = 34)	10 (37.0) (n = 27)	0.22
Heart	5 (29.4) (n = 17)	6 (31.6) (n = 19)	1.00
Liver	2 (50) (n = 4)	1 (25) (n = 4)	1.00

CR = complete response; NR = no response; PR = partial response; VGPR = very good partial response.

numerically, but not statistically, higher CR rate compared with the MD group (27.6% vs 8.0%; $P = 0.14$). The median time to achieve a PR or better was also not significantly different between the CTD and MD groups (2.5 vs 2 months; $P = 0.68$; data not shown).

Organ response assessment required involvement of the organ at the moment of treatment onset. Totals of 61, 36, and 8 patients were eligible for renal, cardiac, and hepatic response assessments, respectively, with no significant differences between the 2 groups (Table II). Further analysis of renal response revealed that the CTD group achieved a similar renal response rate (52.9% vs 37.0%, $P = 0.22$), with no differences versus the MD group at any time point (Table III). The difference in renal function after the end of treatment was not significant between the 2 regimens.

To analyze the effects of hematologic response on organ response, we combined the 2 groups. Of the 20 patients who achieved a PR after the second cycle of treatment, 15 patients (75%) achieved response in at least 1 organ compared with 12 of 34 patients (35.3%) with no response. This finding implies that

Table III. Decreases from baseline in urinary protein excretion (UPE).

Variable	CTD Group (n = 38)	MD Group (n = 30)	*P*
24-h UPE, median (range), g			
3 mo	0.580 (−0.690 to 2.180) (n = 27)	0.095 (−1.230 to 1.645) (n = 21)	0.39
6 mo	0.730 (0.205−1.587) (n = 17)	0.438 (−0.083 to 1.650) (n = 12)	0.57
12 mo	1.088 (0.621−3.311) (n = 16)	1.095 (0.051−5.272) (n = 11)	0.77
After treatment end	0.678 (0.224−1.833) (n = 31)	0.142 (−0.986 to 1.738) (n = 22)	0.42
No. (%) of patients with a decrease in 24-h UPE of >50% at 12 mo	10 (62.5) (n = 16)	5 (45.5) (n = 11)	0.45
No. (%) of patients with a decrease in eGFR of >25% at 12 mo	3 (17.6) (n = 17)	1 (9.1) (n = 11)	1.00

eGFR = estimated glomerular filtration rate.

achieving a PR after the second cycle of treatment is an important predictive factor for organ response (odds ratio = 5.5; 95% CI, 1.6−18.9; $P = 0.005$) (data not shown).

Survival

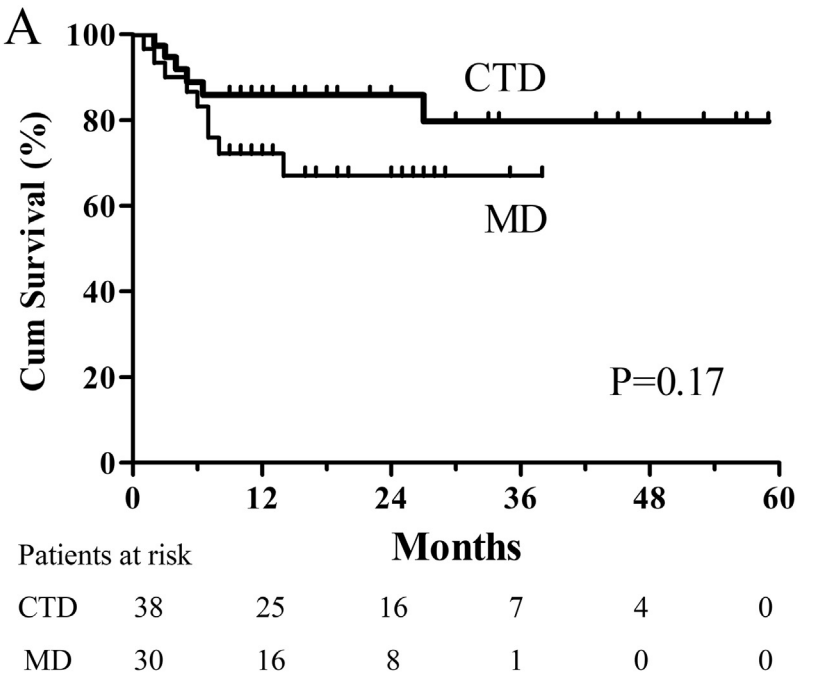
At the cutoff date of April 1, 2018, 6 patients in the CTD group and 9 patients in the MD group died during the follow-up period based on disease progression. Among these, 2 in the CTD group and 3 in the MD group died within 12 weeks (all were assessed as having 2012 Mayo stage III). None of the deaths were considered by the investigators as treatment related. In the surviving patients, the median follow-up times from chemotherapy were 22 and 17 months in the CTD and MD groups, respectively ($P = 0.34$) (data not shown).

The OS and PFS in all patients are listed in Figure 1. Based on the Kaplan-Meier survival analysis, the estimated median OS from the start of treatment was not reached in either group, and the difference between the 2 groups was not significant ($P = 0.17$). The cumulative survival rates at the end of 6, 12, and 36 months of treatment were 88.9%, 85.8%, and 79.7% in the CTD group and 83.2%, 72.2%, and 67.0% in the MD group. After adjusting for the number of organs involved, alkaline phosphatase level, Mayo stage, interventricular septal thickness, and NT-proBNP in the multivariate analysis, there were no differences in OS between the 2 regimens (Table IV).

Sixty-four patients were eligible for PFS assessment. The median PFS values were 36 months with CTD and 14 months with MD ($P = 0.24$) (Figure 1B). To further analyze the effect of each regimen in patients with serious organ involvement, we assessed OS in patients with cardiac involvement and/or Mayo stage >I. In 44 patients with cardiac involvement, median OS was not reached, and the 36-month cumulative survival rates were 75.8% in the CTD group and 67.9% in the MD group (Figure 2A). In the group of 38 patients with Mayo stage >I, similarly, median OS was also not reached, and the 36-month cumulative survival rates were 69.8% and 65.0% in the CTD and MD groups, respectively (Figure 2B). There were no deaths reported among the patients who achieved VGPR or CR.

Safety Profile

Toxicities of grade ≥2 observed in our study are shown in detail in Table V. Aside from the deaths from disease progression, no other toxicities of grade



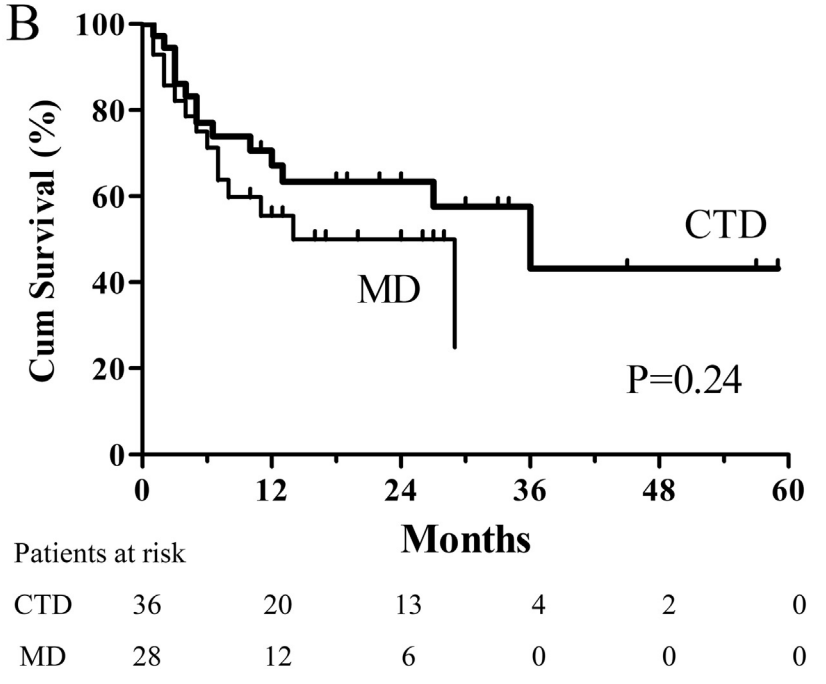


Figure 1. Overall (A) and progression-free (B) survival in all patients according to treatment group.

Table IV. Univariate and multivariate analyses of factors associated with overall survival.

Variable	Univariate		Multivariate	*P*
	HR (95% CI)	*P*	HR (95% CI)	
Age	0.966 (0.916−1.019)	0.20	NI	
Male	1.496 (0.532−4.206)	0.45	NI	
No. of organs	3.988 (1.531−10.388)	0.005	4.309 (0.773−24.021)	0.10
CTD	0.494 (0.175−1.397)	0.18	0.673 (0.172−2.633)	0.57
κ Subtype	1.234 (0.421−3.616)	0.70	NI	
ALP	1.002 (1.001−1.003)	0.001	1.001 (0.9999−1.003)	0.07
eGFR	1.005 (0.980−1.030)	0.72	NI	
dFLC	1.009 (0.998−1.020)	0.10	NI	
Mayo stage	2.949 (1.458−5.965)	0.003	0.814 (0.264−2.508)	0.72
IVS	1.357 (1.165−1.581)	<0.001	1.477 (1.167−1.868)	0.001
NT-proBNP of >8500 ng/L	7.247 (2.153−24.400)	0.001	6.006 (1.355−26.62)	0.02

ALP = alkaline phosphatase; CTD = cyclophosphamide + thalidomide + dexamethasone; dFLC = difference between involved and uninvolved free light-chain; eGFR = estimated glomerular filtration rate; IVS = interventricular septal thickness; NI = not included; NT-proBNP = N-terminal brain natriuretic peptide.

4 or 5 (ie, severe) were recorded. The difference in the total numbers of patients experiencing adverse events between the CTD and MD cohorts was not significant (60.0% vs 59.3%; $P = 0.95$). However, fatigue occurred more frequently in patients who received CTD than in those treated with MD (48.5% vs 21.7%; $P = 0.04$). Constipation occurred in both groups with a relatively high prevalence (24.2% vs 26.1% in the CTD and MD groups, respectively; $P = 0.88$). Serious arrhythmias and toxicities of grade 4 or 5 were not observed during our follow-up period. The therapeutic regimen was discontinued due to adverse events in 3 patients (1 due to fatigue in the CTD group vs 2 due to anemia in the MD group; $P = 0.75$).

DISCUSSION

In China, systemic AL amyloidosis is a rare disease with a low awareness and a nonspecific presentation of symptoms. The long interval required for diagnosis (6 months at our center), multiorgan involvement (76.5%), advanced age (mean, 57.3 years), and lack of effective chemotherapy lead to a high risk for mortality.[5,23] Early diagnosis and prompt treatment are crucial in obtaining a better outcome. With the development of novel agents and their use in combination, the outcomes in patients with AL amyloidosis have greatly improved,[24,25] although outcomes are still poor when there is cardiac involvement.[26] Although some targeted agents such as antibodies for serum amyloid P component[27] have been studied, evidence for their widespread use falls short and is limited to clinical trials. Moreover, no drug therapy has been approved by the US Food and Drug Administration or the European Medicines Agency for the treatment of AL amyloidosis. At present, only limited clinical trials have evaluated outcomes with different regimens.[24,28] Oral MD is still the standard chemotherapy with the highest level of evidence,[8] but the median time to achieve a response is 4.5 months.[12] Moreover, patients in China appear to have some difficulty acquiring melphalan. In 2007, Wechalekar et al[11] reported that among 34 responders who used the CTD strategy, all achieved a PR by the end of the third month of treatment. Furthermore, they demonstrated rapid clonal control, which is essential for preserving organ function and improving survival.[29,30] CTD had been the standard of care for a long time before bortezomib was widely used in England. Nonetheless, there are very few reports comparing CTD with other regimens,[31,32] especially with the standard oral MD.

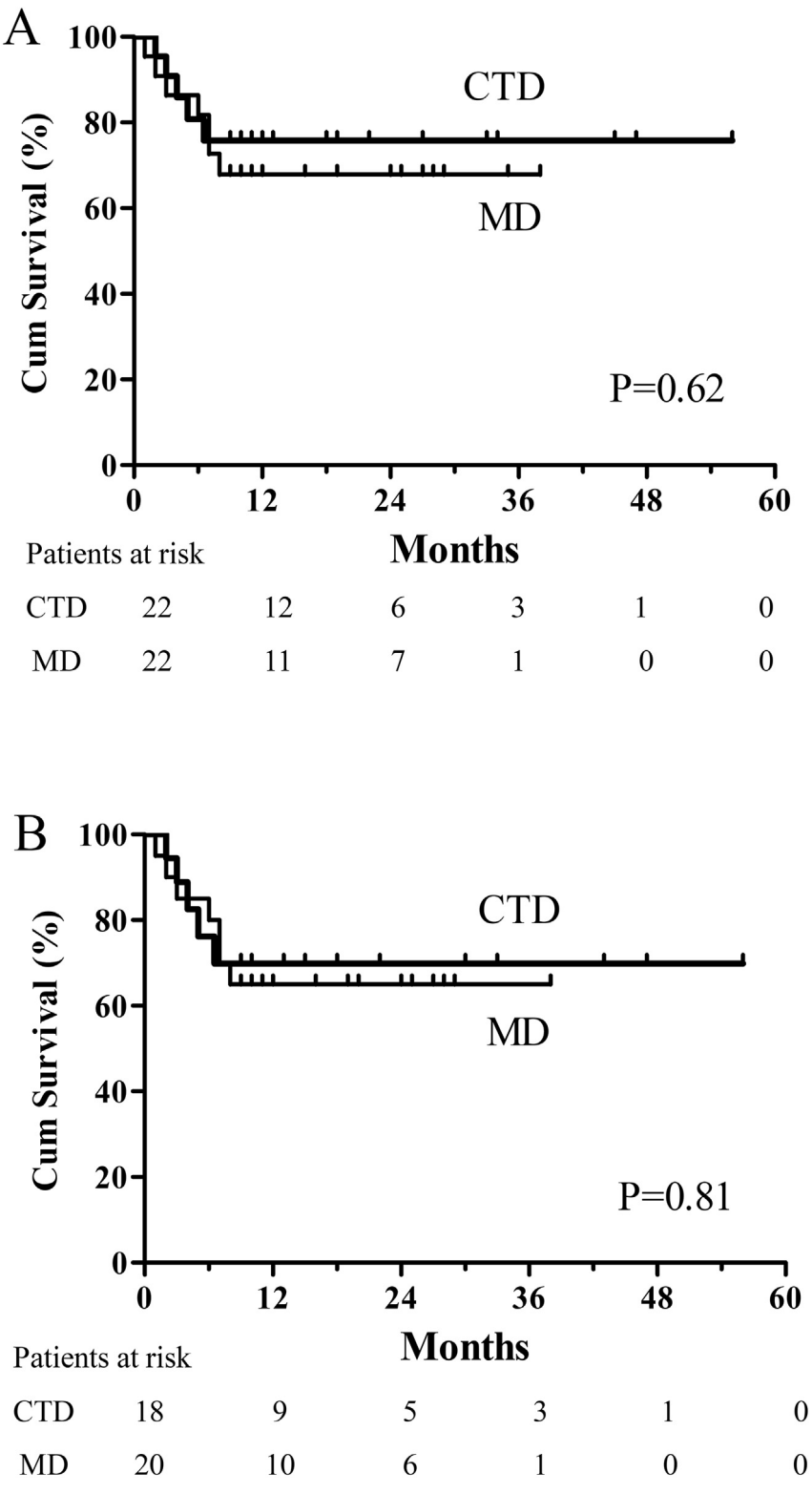


Figure 2. Overall survival according to treatment group among patients with cardiac involvement (A) and Mayo stage >I (B).

Table V. Prevalences of adverse events of grade ≥2. Data are given as number (%) of patients.

Parameter	CTD Group* (n = 38)	MD Group† (n = 30)	P
Event			
Fatigue	16/33 (48.5)	5/23 (21.7)	0.04
Constipation	8/33 (24.2)	6/23 (26.1)	0.88
Nausea/vomiting	4/33 (12.1)	4/23 (17.4)	0.87
Syncope	4/33 (12.1)	2/23 (8.7)	1.00
Anemia	3/35 (8.6)	6/27 (22.2)	0.25
Peripheral neuropathy	3/33 (9.1)	0/23	0.38
Febrile neutropenia	2/35 (5.7)	5/27 (18.5)	0.24
Respiratory system infection	2/33 (6.1)	1/23 (4.3)	1.00
Herpes zoster virus	1/33 (3.0)	0/23	1.00
Tremor	1/33 (3.0)	0/23	1.00
Depressed platelet count	0/35	4/27 (14.8)	0.07
Urinary system infection	0/33	1/23 (4.3)	0.41
Ventricular arrhythmia	0/35	0/27	NA
Treatment-related death	0/38	0/30	NA
Withdrawal from treatment due to adverse event	1/33 (3.0)	2/23 (8.7)	0.75
Toxicities of grade 4 or 5‡	0/33	0/23	NA
Total	21/35 (60.0)	16/27 (59.3)	0.95

NA = not available.
* In 2 patients in this group, only laboratory values (biochemistry and ECG) were available for the recording of adverse events; data on other events were not available.
† In 4 patients in this group, only laboratory values (biochemistry and ECG) were available for the recording of adverse events; data on other events were not available.
‡ Severe toxicities. Death (any cause) occurred in 6 and 9 patients in the CTD and MD groups, respectively. Among these, 2 patients in the CTD group and 3 in the MD group died within 12 weeks (all were assessed as having 2012 Mayo stage III). None of the deaths were considered by the investigators as treatment related.

In our center, we recommend bortezomib + dexamethasone, CTD, or MD as first-line therapy. The choice of different regimens is based on the physician's experience. The mean age of the patients in our center is 57.3 years, which is younger than the mean age of 73.5 years[2] or 62 years[33] previously reported in Western countries, but similar to the mean age of 56 years reported in China.[34]

The study conducted in our center shows a similar CR in the CTD group as in the MD group (27.6% vs 8.0%; $P = 0.14$), a finding similar to one from a previously reported trial, in which CR was achieved in 7 patients with CTD (58.3%; 95% CI, 28%−85%) and in 3 patients with MD (25.0%; 95% CI, 6%−57%).[35] The numerically but not statistically higher levels of cardiac biomarkers, greater tumor burden (dFLC), and worse Mayo staging in the MD group may have contributed to this phenomenon. CR occurred in 2 patients (8.0%) who received MD in the present study, which lags behind the reported 33% in patients treated with the MD regimen in a previous study.[12] The shorter median follow-up time in the MD group in the present study may have accounted for this difference. With further analysis, we found that even though some patients had reached the criterion of normalization of free light-chain levels and ratio for a long period after the intervention, positive serum immunofixation persisted.

Most recently, Siegismund et al[36] reported that intramyocardial inflammation is related to increased mortality in AL amyloidosis. In addition to inducing apoptosis of the plasma cells, the antiinflammatory

effect of dexamethasone, through the inhibition of the activity of phospholipase A_2, which is different from the mechanism of the antiinflammatory effect of NSAIDs, may also play a role in organ response.[37] There was no difference between the 2 regimens in terms of cardiac response. A recent study reported that 24-hour urinary protein excretion was an independent risk factor for OS.[38] However, 2 patients who received the CTD regimen had progressive cardiac issues following treatment despite the positive renal response.

The CTD-associated PFS reported here is 36 months, which is apparently longer than the previously reported 14 months.[31] The median OS was not reached in either group. Furthermore, the patients in the high-risk subgroup (cardiac involvement or Mayo stage >I) also did not reach the median OS. This finding may have been in part due to the relatively short follow-up period and the small number of patients. In all patients regardless of risk stratification, there was no significant difference in adjusted OS between the 2 groups, supporting that the CTD regimen may not be inferior to the MD regimen in terms of survival. Moreover, thalidomide, due to its antiangiogenic activity, has been used in clinical trials in the treatment of cancer itself, including multiple myeloma. Its potential benefit in cachexia may also be involved in the survival of patients with AL amyloidosis.[39]

The deaths in our cohort were not considered treatment related, although a prevalence of 4% was previously reported with CTD.[11] This finding may have occurred because treatment regimens were discontinued for a period if there were any signs of serious adverse events. All of the adverse events that were reported provide further evidence of the tolerability of both regimens. Among the events collected, fatigue was the more common in the CTD group than in the MD group ($P = 0.04$). Contrary to the findings described in a previous article regarding significant toxicity,[40] no adverse events were reported in the 3 patients who received thalidomide monotherapy (100 mg/d) as maintenance therapy after achieving CR.

Given the retrospective nature of this study, these results should be interpreted with caution. The selection bias regarding the treatment regimen was unavoidable since economic factors, the severity of illness, and physician's advice and recommendations all affect the choice of regimens. Furthermore, the long-term prognosis could not be evaluated because of the short duration of the follow-up and the small size of the study sample. In addition, obtaining an accurate diagnosis of AL amyloidosis is crucial for effective therapy. We combined the immunofluorescence results detected in tissue with serum/urine M protein to diagnose AL amyloidosis. However, the use of commercial antibodies for typing amyloidosis may lead to erroneous results.[41] It would have been better if we had implemented immunoelectron microscopy, mass spectrometry, or DNA testing for typing amyloidosis. Nonetheless, although this study was of retrospective and negative-control design with some limitations, it may provide a therapeutic option for use in developing countries where patients cannot afford bortezomib or melphalan.

Although oral CTD has been the standard of care in the United Kingdom over the past decade, the MD regimen is recommended by the Mayo Clinic as a first-line choice in patients who are ineligible for ASCT.[8] The rare prevalence of AL amyloidosis makes it difficult to conduct a large-scale clinical trial. The findings from our study indicate that the CTD regimen may be associated with a higher rate of remission of 24-hour proteinuria than that with the MD regimen in systemic AL amyloidosis with kidney involvement. However, long-term survival is unknown and remains to be determined. Moreover, different organ responses were out of sync. All of these issues need to be addressed in a prospective, randomized trial.

CONCLUSION

The CTD regimen may be an effective and well-tolerated therapy and is not inferior to standard oral MD, especially in patients with renal AL amyloidosis.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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