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CLINICAL STUDY

Outcomes of BTD vs. BCD as initial treatment of renal amyloid light-chain amyloidosis: a retrospective cohort study in China

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ABSTRACT

Objectives: To compare the efficacy and safety of bortezomib with thalidomide and dexamethasone (BTD) and bortezomib with cyclophosphamide and dexamethasone (BCD) as the initial treatment for renal amyloid light chain (AL) amyloidosis in Chinese cohort.

Methods: A cohort of 174 patients with AL amyloidosis was studied in Guangdong Provincial People's Hospital from January 2008 to August 2023. Propensity-score matching cases were applied to assess the outcomes of patients treated with BTD and BCD regimen. Primary outcomes were patients achieving hematologic response and organ responses, and the secondary endpoints were patients progressing to end-stage renal disease or all-cause death.

Results: 44 Patients were included. The hematologic complete response rate (CR) in the BTD group was comparable between the groups of BTD group and BCD. However, the time to achieve hematologic CR was significantly shorter in the BTD group compared to the BCD group (4.97 vs. 7.71 mon, $p=0.010$). Furthermore, when reaching hematologic response, the cumulative dose of bortezomib that standardized by body surface area (BSA) was lower in BTD group than in the BCD group (10.4 vs. 15.6 mg/m^2, $p=0.013$). There was no significant difference of renal and cardiac response between groups. However, post-treatment proteinuria levels after treatment were significantly lower in the BTD group compared to those in the BCD group (747 mg/24h vs. 2928 mg/24h, $p=0.048$).

Conclusions: Compared to BCD regimen for renal AL amyloidosis, initial treatment with BTD regimen demonstrated similar rates of hematologic CR but showed superior reduction in proteinuria, reduced cumulative dose of bortezomib and faster time-to-response.

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Introduction

Amyloidosis encompasses a group of disorders characterized by the deposition of amyloid in the extracellular matrix, resulting in tissue and organ damage, including the kidney, heart, liver, skin, and peripheral nerves. Currently, more than 42 different proteins have been identified to be involved in this process. Among them, light chain (AL) amyloidosis is the most prevalent systemic form that can be ameliorated through chemical treatment [1]. AL amyloidosis is the most commonly diagnosed form of systemic amyloid disease in China. The incidence of AL amyloidosis is on the rise, likely due to a combination of improved diagnostic techniques and aging population. Therefore, it is crucial to develop an optimal therapeutic regimen for Chinese patients with AL amyloidosis that can reduce mortality rates and improve their quality of live [2].

The kidney is the organ most frequently affected in this context. In the kidney, amyloidosis predominantly initiates within the mesangium, progressively disseminating to impact various renal architectures. The predominant glomerular localization of amyloid deposits is observed most frequently, which precipitates substantial nephrotic syndrome proteinuria [3]. Conversely, when amyloid load is predominantly contained within arterial

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and arteriolar structures, the degree of proteinuria is reduced, and patients frequently present with manifestations of renal insufficiency. It is postulated that extensive glomerular and vascular amyloid deposition contributes to interstitial fibrosis/tubular atrophy, ultimately underpinning the pathogenesis of renal failure [4]. Amyloid deposition can also be found in the renal interstitium and tubular basement membrane, reflecting the load and damage caused by the light chain in the kidney [5]. In a study involving 474 patients, proteinuria and renal insufficiency were observed in 73% of the participants [6]. Another study with 145 patients found that those presenting renal symptoms had a significantly higher likelihood of developing end-stage renal disease (ESRD) compared to those without such symptoms (42% versus 5%) [4]. A similar incidence of ESRD (39%) and median survival on dialysis was reported in an Italian analysis focusing on biopsy-proven renal AL patients [5]. The median survival time after initiating dialysis was merely 10.4 months, with approximately 20% of patients succumbing within the first month.

The therapeutic goal of AL amyloidosis therapy is to destroy monoclonal plasma cells in order to eliminate the production of toxic light chain of amyloidosis [7]. Bortezomib is actually an inhibitor targeting the proteasome, which can selectively bind to the active site of the proteasome, block the degradation of the target protein by the protease, and inhibit the progression of AL amyloidosis.

The utilization of bortezomib has become the established therapeutic approach in AL amyloidosis. Initial studies have reported favorable hematologic responses, with an overall response rate (ORR) ranging from 60 to 94%, and a complete hematologic response (CR) rate ranging from 23 to 71% [8–10]. However, a multicenter retrospective European study concluded that upfront administration of bortezomib-cyclophosphamide dexamethasone (CyBorD) failed to improve outcomes in Mayo stage III disease, resulting in a median survival of only 4.6 months and a CR rate of merely 17% [11]. Therefore, this study aimed to retrospective assess the efficacy and safety of BTD as the initial treatment for renal AL amyloidosis in China cohort while providing additional clinical evidence for establishing standard therapeutic approaches.

Methods

Patients

This is a retrospective, single-center study conducted at Guangdong Provincial People's Hospital, involving patients with renal AL amyloidosis confirmed by biopsy. A total of 174 patients were screened for eligibility between January 2008 and August 2023 (Figure 1). Amyloidosis was confirmed by deposits of Congo red positive fibers and spotless fibers 8–10 nm in diameter. The choice of treatment is based on the doctor's

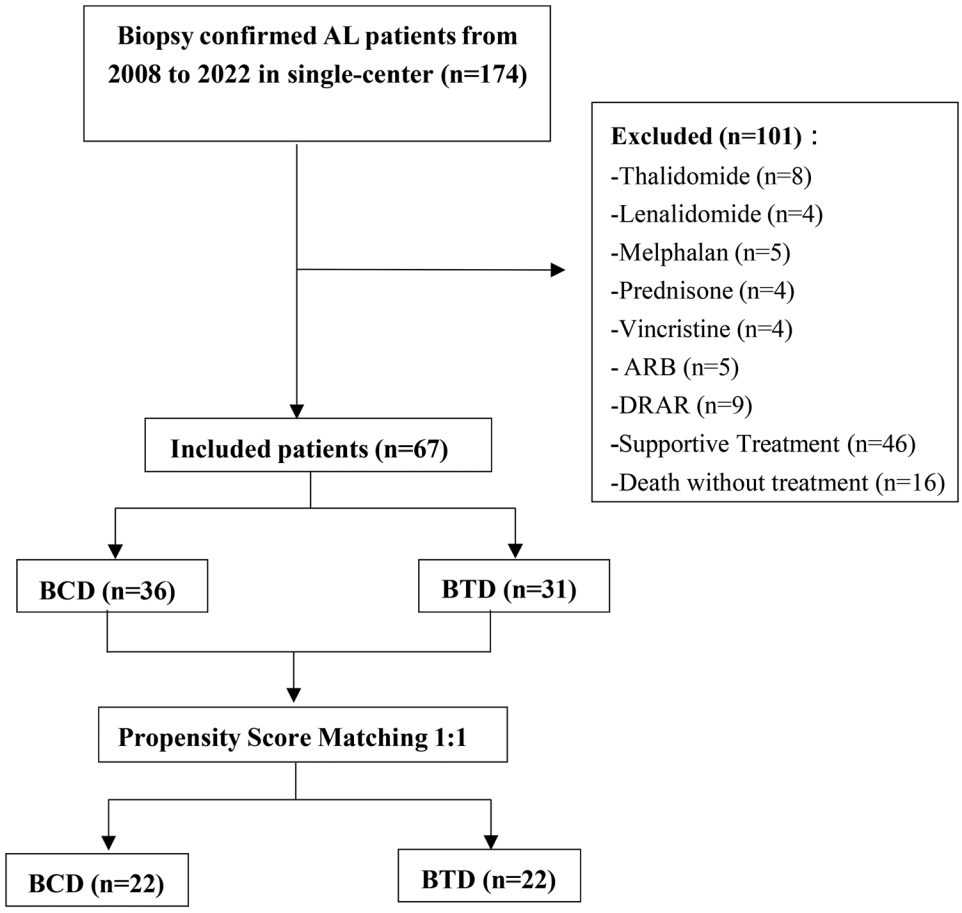

Figure 1. Patient enrollment flow chart. Abbreviations: BCD: bortezomib and cyclophosphamide and dexamethasone; BTD: bortezomib and thalidomide and dexamethasone; AL: light chain amyloidosis; ARB: angiotensin receptor blocker.

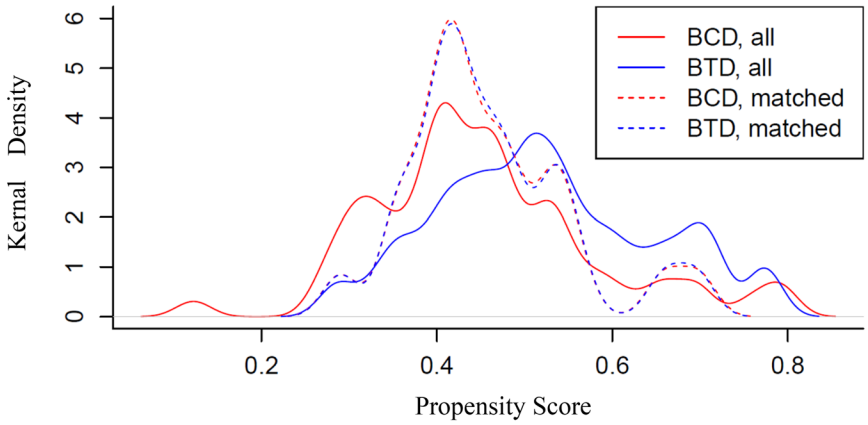

Figure 2. Kernal density plots. Propensity score distribution of cohorts of patients with AL using BCD or BTD therapy before and after PSM pairing.

advice and the patient's discretion. Among them, 101 patients were excluded due to the use of alternative chemotherapy (malphalan and prednison), supportive treatment administration, or diagnosis of multiple myeloma. Ultimately, a final cohort of 67 patients enrolled. We used 1:1 propensity score-matching (PSM) to match BCD or BTD regimen groups because PSM is helpful to balance the potential selection bias, confounding, and differences between treatment groups in observational studies. The variables that were matched included clinical characteristics: sex, age, baseline urinary protein, baseline eGFR, baseline serum free light chain, Mayo staging (Figure 2). Finally, we ended up with 22 pairs of patients, 22 patients in the BTD group and 22 patients in the BCD group.

All included patients met the following diagnostic criteria: positive Congo red staining in renal pathological biopsy; confirmation of light chain amyloidosis through immunofluorescence, immunohistochemistry or mass spectrometry [1].

Chemotherapy regimen

The BTD regimen consisted of 1.3 mg/m^2 bortezomib administered subcutaneously on days 1, 8, 15, 22; combined with thalidomide 100 mg/day orally and 40 mg dexamethasone administered intravenously or orally on days1–2, 8–9, 15–16, 22–23. Therapy with BCD was composed of bortezomib and dexamethasone at the same dose and schedules as for the BTD regimen plus 900 mg/m^2 cyclophosphamide administered intravenous injection on days 1~2. The two regimens had a cycle of 28 days. Recommended concomitant medications included gastric mucosa protective agents, antiviral drugs, anticoagulant or antiplatelet drugs, diuretics, various types of myocardial protective drugs and antiarrhythmic therapy were used according to the patient's situation.

Assessment

The primary endpoint of the study was patients achieving hematologic response and organ responses, and the secondary endpoint was patients progressing to end-stage renal disease or all-cause death. All patients were followed up until August 2023. Efficacy evaluation was divided into hematologic and organ responses. The criteria for evaluating the hematological response came from NCCN Guidelines Version 1.2017 Systemic Light Chain Amyloidosis. Complete response (CR): normalization of the free light chain levels and ratio, negative serum and urine immunofixation. Very good partial response (VGPR): reduction in the dFLC to <40 mg/L. Partial response (PR): a greater than 50% reduction in the dFLC. No response: less than a PR. Progression: from CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double); From PR, 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M protein to >200 mg/d (a visible peak must be present); Serum free light chain increase of 50% to >100 mg/L. Organ responses were divided into response or progression. Guidelines from China state that the criteria for remission in patients with renal involvement are $a \geq 50\%$ decrease in urinary protein levels from pretreatment levels and $a < 25\%$ increase in serum creatinine from pretreatment baseline levels [1]. The occurrence of edema, infection, peripheral neuropathy, gastrointestinal reactions and other adverse events during treatment was recorded.

Statistical analysis

SPSS 21.0 was used for statistical analysis. Continuous variables are measured by mean (standard deviation) or median (quartile range; IQR). The classification data are expressed by frequency. *T* test was used for inter-group comparison of measurement data consistent with normal distribution. Measurement data of non-normal distribution were represented by M, and comparison between groups was performed by Mann-Whitney *U* test. Counting data were expressed as percentages, and chi-square test was used for comparison between groups. Survival curves were plotted using the Kaplan-Meier method and compared with the log-rank test. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Among total 174 AL amyloidosis patients with a median age of 59 years and lambda type light chain was the

predominant involved light chain (76.1%), 62.6% of them was male. Of the patients with renal involvement, 60.1% had a baseline estimated glomerular filtration rate ≥60 mL/min/1.73m^2 (CKD-EPI formula), and the median 24-h urinary protein quantitation was 4.7 g. Mayo Stage I accounted for 49.2% of patients, followed by Mayo stage II (29.1%), Mayo stage III (15.4%), and Mayo stage IV (6.3%). A total of 101 excluded patients did not receive a standard treatment regimen with bortezomib as the primary agent. During follow-up.

As summarized in Tables 1 and 2, among the patients using bortezomib as the initial chemotherapy regimen, we matched a final cohort of 44 patients: BCD group ($n=22$) and BTD group ($n=22$). No significant differences of baseline clinical characteristics were observed between the two groups. Considering the potential side effects, dexamethasone's dosage was adjusted according to every single individual's condition in both groups, which resulted in a full dose administration to only eleven patients at doses equivalent to or exceeding 320 mg/per cycle compared to fourteen individuals in the BTD group (50.0 vs. 63.6%, $p=0.048$).

Hematologic and organ responses

The hematologic CR rate in the BTD group was same as that in the BCD group (86.3 vs. 81.8%, $p=0.649$). Among Mayo Stage I patients, hematologic CR rate was 90% in the BCD group, 100% in the BTD group ($p=0.500$), and 75 and 77.8% in stage II patients ($p=0.727$). We counted the cumulative dose of bortezomib that standardized by BSA (body surface area) when patients reached hematologic response. The cumulative dose of bortezomib in the BTD group was less than that in the BCD group (10.4 vs. 15.6 mg/m^2, $p=0.013$). When hematologic responses were achieved, the median period of treatment in the BCD group was 3 cycles, with a mean of 4.52 cycles, and the median period of treatment in the BTD group was 2 cycles, with a mean of 2.67 cycles. There was no statistically significant difference between the two sets of data (3 vs. 2 $p=0.742$, 4.52 vs. 2.67, $p=0.143$). In contrast, time to reached hematologic complete response in the BTD group was shorter than the BCD group (4.97 vs. 7.71 months, $p=0.010$).

Renal and cardiac response in BTD group were slightly but not significantly higher than those in BCD group (renal 59.1 vs. 50.0%, $p=0.446$; cardiac 23.1 vs. 10.0%, $p=0.588$). The median time to renal response was 16 months in the BCD group and 12 months in the BTD group ($p=0.735$). 24h Proteinuria in the BTD group was markedly lower than BCD group after treatment (747 mg/24h vs. 2928 mg/24h, $p=0.048$). In BCD group, one

Table 1. Clinical characteristics of 174 AL patients at diagnosis.

Characteristic	AL patients
Male (n, %)	109 (62.6%)
Age (years)	59.0 (53.0–65.0)
<65 y	136 (78.2%)
≥65 y	38 (21.8%)
Organ involvement (*n*, %)	
Kidney	124 (71.3%)
Cardiac	98 (56.3%)
>1 Organ involved	118 (67.8%)
iFLC (*n*, %)	
Kappa	29 (23.9%)
Lambda	92 (76.1%)
Creatinine (μmol/L)	87.8 (66.5–123.5)
eGFR (mL/min/1.73m^2)	77.1 (46.0–96.5)
<60 (*n*, %)	52(29.9%)
≥60 (*n*, %)	122(60.1%)
24h Proteinuria (g/d)	4.7 (2.2–7.7)
NT-proBNP (pg/ml)	1137 (33.55–4826.75)
cTnt (ng/L)	45.1 (25.83–79.55)
dFLC (mg/L)	123.16 (50.39–300.56)
Positive serum immunofixation (*n*, %)	121 (69.5%)
IVS thickness (mm)	12.5 (11.0–14.35)
Marrow plasma cell (*n*, %)	6 (3–10)
Mayo clinical 2012 stage	
Stage I (*n*, %)	86 (49.2%)
Stage II (*n*, %)	51 (29.1%)
Stage III (*n*, %)	27 (15.4%)
Stage IV (*n*, %)	10 (6.3%)

Data are expressed as the mean ± s.d., median (interquartile range), or percentage.

Abbreviations: cTnt: cardiac troponin; eGFR: estimated glomerular filtration rate; iFLC: involved free light chain; dFLC: difference between involved and uninvolved free light chain; NT-proBNP: *N*-terminal pro-natriuretic peptide type B; IVS: interventricular septal.

Table 2. Clinical characteristics of included 44 AL patients at diagnosis.

Characteristic	BCD ($n=22$)	BTD ($n=22$)	*p* Value
Male (*n*, %)	11 (50.0%)	14 (63.6%)	1.00
Age (years)	60.5 (54.25–63.75)	56 (46.75–61.5)	0.103
Organ involvement (*n*, %)			
Kidney	22 (100%)	22 (100%)	1.00
Cardiac	10 (45.4%)	13 (59.1%)	0.709
>1 Organ involved	15 (68.2%)	17 (77.3%)	0.424
iFLC (*n*, %)			
Kappa	3 (13.6%)	3 (13.6%)	1.00
Lambda	19 (86.4%)	19 (86.4%)	1.00
Creatinine (μmol/L)	80 (65.0–130)	73.61 (56.64–92.74)	0.489
eGFR (mL/min/1.73m^2)	86.29 (58.16–91.73)	92.56 (79.2–107.37)	0.195
<60 (*n*, %)	5 (22.7%)	3 (13.6%)	
≥60 (*n*, %)	17 (77.3%)	19 (86.4%)	
24h Proteinuria (g/d)	5.0 (3.4–7.4)	4.63 (2.45–7.8)	0.960
<5 (*N*, %)	12 (54.6%)	13 (59.1%)	
≥5 (*n*, %)	10 (45.4%)	9 (40.9%)	
NT-proBNP (pg/ml)	612.5 (75.75–2326.5)	117.25 (53.5–917.42)	0.239
cTnt (ng/L)	56.5 (47.5–67.6)	22.7 (13.25–50.12)	0.028
dFLC (mg/L)	113.22 (20.92–268.57)	54.03 (32.8–178.13)	0.424
Positive serum immunofixation (*n*, %)	18 (81.8%)	16 (72.7%)	0.954
IVS thickness (mm)	11 (10–13)	11.25 (10–12.45)	0.181
Marrow plasma cell (*n*, %)	6 (4–8)	5 (3–6)	0.170
t(11,14) Positive (*n*, %)	3 (13.6%)	6 (27.3%)	0.133
Mayo clinical 2012 stage			
Stage I (*n*, %)	10 (45.4%)	9 (40.9%)	0.812
Stage II (*n*, %)	8 (36.4%)	9 (40.9%)	0.977
Stage III (*n*, %)	3 (13.7%)	3 (13.7%)	0.259
Stage IV (*n*, %)	1 (4.5%)	1 (4.5%)	1.00
Dexamethasone (mg per cycle)			
320 (*n*, %)	11 (50.0%)	14 (63.6%)	0.722
160 (*n*, %)	9 (40.9%)	8 (36.4%)	0.948
<160 (*n*, %)	2 (9.0%)	0	

Data are expressed as the mean ± s.d., median (interquartile range), or percentage.

Abbreviations: cTnt: cardiac troponin; eGFR: estimated glomerular filtration rate; iFLC: involved free light chain; dFLC: difference between involved and uninvolved free light chain; NT-proBNP: *N*-terminal pro-natriuretic peptide type B; IVS: interventricular septal.

patient progressed in death and one another patient progressed into MM after 3 years of drug withdrawal when she reached hematologic complete response. None of above was seen in BTD group, were shown in Tables 3 and 4.

Survival

The median follow-up time in the cohort was 13.2 months for the BTD group and 25.6 months for the BCD group. Among the 44 patients, only one patient died in BCD group during the follow-up period. One and 2-year OS was 81.7%, respectively in patients who received the BTD regimen, vs 82.7% in patients who received the BCD regimen. There were no significant differences in OS were observed in two groups ($p=0.310$, Figure 3).

Toxicity

The incidence of peripheral edema, infection, granulocytopenia, thrombocytopenia and gastrointestinal reactions in BTD group was almost same as that in BCD group. The total

Table 3. Hematologic and organ responses in 44 AL patients.

	BCD ($n=22$)	BTD ($n=22$)	p Value
Hematologic response			
Complete response (n, %)	18 (81.8%)	19 (86.3%)	0.649
Very good partial response (n, %)	3 (13.6%)	2 (9.1%)	0.865
Partial response (n, %)	1 (4.5%)	1 (4.5%)	1.00
Stable disease	0	0	
Progressive disease	0	0	
Relapse	1	0	
Time to CR achieved (mon.)	7.71	4.97	0.010
Cycles for CR achieved (n)	3	2	0.742
Dose of Bortezomib for CR (mg/ m^2)	15.6 (15.6–20.8)	10.4 (10.4–15.6)	0.013
Mayo clinical 2012 stage CR			
Stage I (n, %)	9/10 (90.0%)	9/9 (100%)	0.500
Stage II (n, %)	6/8 (75.0%)	7/9 (77.8%)	0.727
Stage III (n, %)	3/3 (100%)	2/3 (66.6%)	1.00
Stage IV (n, %)	0/1	1/1 (100%)	
Organ response			
Kidney response (n, %)	11/22 (50.0%)	13/22 (59.1%)	0.446
Progression to dialysis (n, %)	5/22 (22.7%)	1/22 (4.5%)	0.588
Time to kidney response (mon.)	16 (10–16)	12 (11–16)	0.735
Cardiac response (n, %)	1/10 (10.0%)	3/13 (23.1%)	0.588
Cardiac progression (n)	1	0	
Progression to multiple myeloma (n)	1	0	
Death (n)	1	0	

Table 4. Kidney related biochemistry indicators before and after treatment.

	BCD		BTD		
	Before	After	Before	After	p Value
Creatinine (μmol/L)	74 (63.68–90.25)	97.67 (59.9–515)	73.61 (55.62–95.18)	88.2 (68.6–111)	0.477
eGFR (ml/min/1.73m^2)	86.29 (58.16–91.73)	64.34 (23.97–100.55)	92.56 (79.2–107.37)	92.88 (58.22–105.62)	0.135
24h Proteinuria (mg)	6989 (2966–9033)	2928 (1347–5899)	5270 (2309–8551)	747 (341–2786)	0.048
ALB (g/L)	21.63 (13.12–29.62)	32.40 (28.31–35.42)	24.1 (19.07–29.95)	35.6 (29.19–39.65)	0.252
Cholinesterase (U/L)	10574(6942–11040)	7270 (6285–9325)	9053 (7735–11057)	7691 (6449–9768)	1.00
DPI (g/kg/d)	0.72 (0.54–0.97)	0.84 (0.74–0.91)	0.83 (0.74–0.97)	0.90 (0.71–1.13)	0.312

Abbreviations: ALB: albumin; DPI: dietary protein intake.

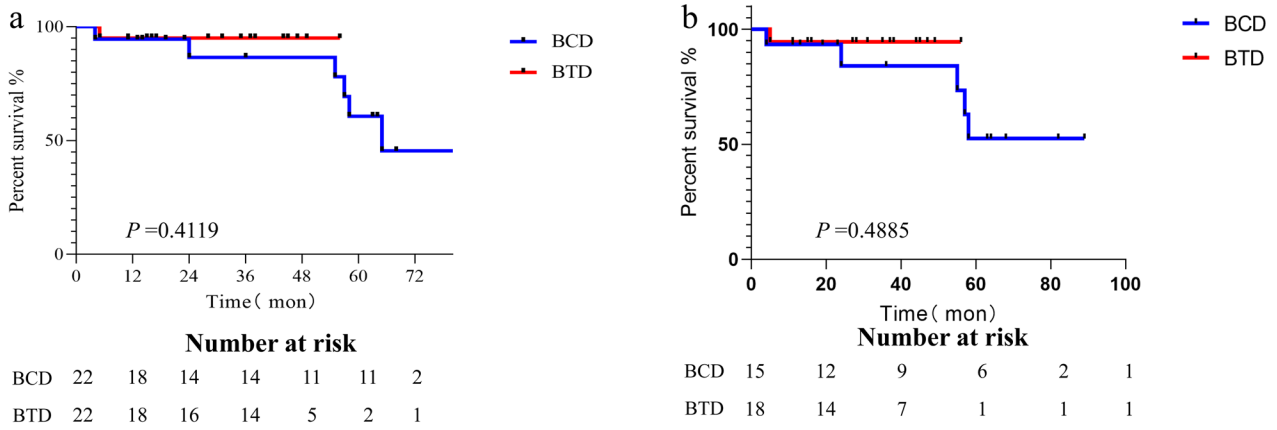

Figure 3. Kaplan–Meier survival curves. (a) Overall survival of patients with AL ($n=44$) according to BCD vs BTD regimen (blue, BCD; red, BTD). (b) Overall survival of patients according to Mayo stage 2012 ≥ II in BCD and BTD regimen (blue, BCD; red, BTD).

Table 5. Adverse events in patients during therapy.

	BCD ($n=22$)	BTD ($n=22$)	p Value
Edema/Oliguresis (n, %)	13 (59.1%)	9 (40.9%)	0.052
Infection (n, %)	7 (31.8%)	5 (22.7%)	0.063
Peripheral neuropathy (n, %)	1 (4.5%)	3 (13.6%)	0.058
Fatigue (n, %)	10 (45.4%)	13 (59.1%)	0.055
Constipation (n, %)	2 (27.3%)	3 (9.1%)	0.057
Nausea (n, %)	5 (22.7%)	4 (18.2%)	0.070
Total events (n)	38	37	0.775

adverse events in the BTD group were lower but not significantly than that in the BCD group [37 vs. 38, $p=0.775$], as shown in Table 5.

Discussion

In current study, we report for the first time that BTD regimen as the initial chemotherapy treatment demonstrated a similar rate of hematologic CR but a significantly superior reduction in proteinuria, less cumulative dose of bortezomib and faster time-to-response compared to BCD regimen for renal AL amyloidosis in Chinese cohort.

The initial chemotherapy regimen for renal AL amyloidosis is continuously improving. With the widespread application of bortezomib-based treatments, the outcomes of renal AL amyloidosis had been much improved. Currently, there were two most commonly employed protocols in clinical practice are bortezomib with dexamethasone (BD) and bortezomib with cyclophosphamide and dexamethasone (BCD). Substantial studies had confirmed the efficacy of BD and BCD regimen in treating both newly diagnosed and relapsed AL patients [8,12–19]. Daratumumab-based therapy has become the first-line treatment for AL amyloidosis, demonstrating rapid hematologic response and better organ response rates [20]. However, Daratumumab-based therapy was more expensive than bortezomib based treatment, and we need to consider Chinese patients' ability to access the drug.

In fact, there were notable differences in the demographic and clinical characteristics of patients at our center compared to reports from Western countries [21,22]. Firstly, our center had a tendency to treat younger patients than those reported in studies conducted in Western countries (mean age 59 vs. 63 years), but similar to another Chinese center (56 years) [23]. Secondly, a greater proportion of patients at our center exhibited lower Mayo stage 2012 scores (<Mayo stage III) (81.8 vs. 43%). Thirdly, there was a higher prevalence of renal involvement among our patients (100 vs. 61%), which can be attributed to the recruitment of patients from the nephrology department. Lastly, AL amyloidosis patients at our center demonstrated favorable renal function (eGFR: 77.1 vs. 64 mL/min/1.73m^2). These discrepancies may partially account for the excellent hematologic and organ response rates observed in our patient cohort.

Although bortezomib combined with thalidomide and dexamethasone (BTD) is a recognized treatment option for multiple myeloma (MM), its efficacy in treating AL amyloidosis has not been established. An European retrospective study compared the effectiveness and safety profiles between BTD therapy and BCD therapy in managing multiple myeloma [24]. Additionally, this investigation revealed that BTD therapy had a higher likelihood to induce severe peripheral neuropathy (PN) than BCD therapy; however, it did demonstrate a greater number of VGPR+CR instances when compared to BCD across all included patients or those categorized as having poor disease stage or high genetic risk. In our study, although there was no statistically significant difference in hematologic complete response rates between the BTD regimen and the BCD regimen, we observed a shorter time to hematologic complete response with the BTD regimen when a higher proportion of patients exhibited genetic t (11,14) translocations. A study retrospectively examined the impact of presence of t (11;14) on outcomes in a population of 135 patients with newly diagnosed AL amyloidosis from United State. These patients received bortezomib as the first-line treatment, and the results demonstrated that patients with amyloidosis with t (11;14) had a poorer OS prognosis [16].

Our findings suggest that BTD therapy achieves hematologic complete response more rapidly with lower doses of bortezomib compared to BCD therapy, thereby reducing patient exposure to immunosuppressive conditions and lowering medical costs. Furthermore, the higher renal response rate observed with BTD therapy highlights the synergistic activity resulting from combining an immunomodulating drug with bortezomib and dexamethasone – an effect previously observed with lenalidomide in the regimen of lenalidomide combined with bortezomib and dexamethasone, which was first described as induction therapy in MM patients back in 2010 [25].

Renal amyloidosis usually presents as a nephrotic syndrome with clinical features of macroproteinuria, hypoproteinemia, and edema [13]. In our study, kidney involvement accounted for 71.3% of patients, and all 44 patients matched in the two groups had kidney involvement. The decline in urinary protein levels indicates the initiation of renal remission and is frequently accompanied by an increase in serum albumin concentrations. However, the recovery of serum albumin in patients with nephropathy is influenced by various factors, including daily dietary protein intake and hepatic synthesis function [26]. Maroni et al. studied the nitrogen balance of 19 patients [27], measured 24-h urine urea, and derived the formula for estimating daily protein intake (DPI) [DPI (g/d) = 6.25 (urine urea +0.031× body weight)]. As presented in Table 4, there were no statistically significant differences observed in cholinesterase levels and DPI calculated based on 24-h urine urea before and after treatment between the two groups, suggesting that the hepatic function and dietary protein intake of both groups were essentially comparable pre- and post-treatment. Consequently, we propose that the primary factor contributing to the recovery of serum albumin in patients with renal amyloidosis is the amelioration of urinary protein.

In 2014, an European study [15] demonstrated that Proteinuria >5 g/24h and estimated glomerular filtration rate (eGFR) <50 mL/min was the most accurate predictors of progression to dialysis. Proteinuria below these thresholds and eGFR above them indicated a low risk of progression (0 and

Table 6. Renal staging in AL amyloidosis and impact on renal survival.

Risk factors	Risk factors present (*n*)	Stage	Patient (%, *n*)		% Of patients on renal replacement therapy at 2y		*p*
			BCD	BTD	BCD	BTD	
Proteinuria > 5g/24h or eGFR <50ml/min/1.73m^2	0	1	27.3% (6)	40.9% (9)	33.3% (2)	0	0.142
	1	2	68.2% (15)	59.1% (13)	13.3% (2)	7.7% (1)	0.896
	2	3	4.5% (1)	0	100% (1)	0	/

4% at 3 years in the testing and validation cohorts, respectively). Conversely, high proteinuria and low eGFR indicated a high risk of progression (60 and 85% at 3 years). The researchers also developed and validated a staging system for renal involvement as well as criteria for early assessment of renal response and progression in AL amyloidosis. As shown in Table 6, our analysis revealed that out of the total patients assessed, according to the kidney stage, 9 patients in the BTD group were classed into stage I and 13patients in stage II, while 6 patients in the BCD group were classed into stage I, 15 patients in stage II and 1 patient in stage III. There was no statistical difference between the two groups. After treatment, only 1 patient in the BTD group progressed to dialysis, while 5 patients in the BCD group progressed to dialysis, including 2 patients in stage I, 2 patients in stage II, and 1 patient in stage III.

Our study had multiple strengths worth highlighting. Firstly, all of the patients included in our study had renal involvement. Our results showed that the renal function of patients in both two therapy was stable before and after treatment, and 24-h urinary protein level in BTD group was lower than that in BCD group. Secondly, our study was single center study, confounding factors were controlled by PSM to compare the effects of the two treatment regimens. It was one of five methods used to control confounding in real-world studies published in Am J Epidemiol. Thirdly, we had carried out multidisciplinary diagnosis and treatment for AL amyloidosis in our center, including nephrology, hematology, cardiology, imaging, pathology and many other related departments. We believed that for patients with different organ or system involvement, refined and comprehensive treatment plan was an important way to improve survival.

The limitation of this study was that it is a single-center retrospective study with a small sample size, which may cause a selection bias because the study was conducted in nephrology department. Our study could not complete demonstrate the advantages of BTD therapy in better renal response. Further studies should be designed to be prospective, with a larger number of cases and a longer observation period to draw more reliable conclusions.

Conclusion

Our data exhibited that BTD regimen as the initial chemotherapy treatment demonstrated a similar efficacy and manageable toxicities as that of BCD in the treatment of renal AL amyloidosis. However, BTD showed the advantages of a lower cumulative dose of bortezomib, shorter time to achieve complete hematological response observed in Chinese cohort. Assessment of response rates in vital organs such as the kidneys and heart may require longer follow-up and larger follow-up cohort. Thus, BTD regimen is supposed as the superior therapeutic option for renal AL amyloidosis of Chinese.

Ethical approval

Ethical approval of this study protocol was obtained by the institutional ethics committee of Guangdong Provincial People's Hospital. All procedures involving human participants complied with the ethical standards and with the principle of the Helsinki Declaration of 1964 and its later amendments in 2008.

Author contributions

We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. Wenjian Wang, Sheng Li, Liye Zhong and Liwen Li contributed to the conception and design of the work. Weiting He, Jianteng Xie and Hok-Him Yau contributed to the acquisition of data, Hok-Him Yau, Yifan Zhang, Shaogui Zhang, Zekun Tan and Xiaojie Chen contributed to analysis and interpretation of data. Wenjian Wang revised the manuscript critically for important intellectual content. All authors have read and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets created during and/or analyzed during the current study will be available from the corresponding author on reasonable request. There is no security, licensing, or ethical issues related to these data.

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