Efficacy and safety of daratumumab plus bortezomib and dexamethasone in newly diagnosed Mayo 2004 stage IIIA or IIIB light-chain amyloidosis: a prospective phase II study

Immunoglobulin light-chain (AL) amyloidosis has shown a rapid and high rate of response to daratumumab, but Mayo stage IIIB patients are excluded from most trials.[1] We aimed to prospectively evaluate the efficacy of daratumumab plus bortezomib and dexamethasone (Dara-VD) in Mayo stage III, especially IIIB, AL through this phase II study (*clinicaltrials gov. Identifier: NCT04474938*). The treatment scheme was intravenous daratumumab at 16 mg/kg weekly in cycles 1-2, every 2 weeks for cycles 3-6 and every 4 weeks for cycles 7-12, 1.3 mg/m^2 bortezomib and 20 mg dexamethasone once weekly for six cycles of 28 days each. The primary outcome was hematologic response ≥ very good partial response (VGPR) at 3 months. A total of 40 patients were enrolled, including 20 with IIIB disease. The percentage of patients with response ≥ VGPR at 3 months was 67.5%, including 47.5% complete response (CR). The percentage who had a cardiac response at 6 months was 47.5%. After a median follow-up of 24.0 months, the 2-year overall survival (OS) estimate reached 69.8%. The response ≥ VGPR at 3 months (70.0%) and cardiac response at 6 months (50.0%) in the IIIB subgroup were comparable to those in the IIIA subgroup. The 2-year OS rate was 65.0% in IIIB patients. Grade ≥3 treatment-related adverse events occurred in 40.0% of patients. Dara-VD had favorable efficacy and safety in advanced AL amyloidosis, including IIIB disease.

As is known, the benefits of bortezomib in severely advanced AL amyloidosis have not been demonstrated definitively.[2,3] In the ANDROMEDA trial, the combination of daratumumab with bortezomib, cyclophosphamide and dexamethasone (Dara-VCD) achieved a deeper hematologic response and longer survival across cardiac stages.[4,5] Unfortunately, patients with stage IIIB disease were excluded from the above study. Agents targeting the deposited amyloid fibrils on affected organs are appealing, but not ready for routine clinical practice.[6,7] Thus, the management of advanced cardiac AL amyloidosis remains a major unmet medical need. The ongoing EMN22 study is evaluating daratumumab monotherapy in stage IIIB patients.[8] Yet past experience has indicated that there might be only one chance to start effective treatment in patients with advanced heart involvement, who have low probability of receiving salvage therapy. Aside from monotherapy, a combination regimen followed by de-escalation is also worth prospective investigation.

Therefore, we conducted this phase II, single-arm study to evaluate the efficacy and safety of front-line Dara-VD in both IIIA and IIIB AL amyloidosis patients (*Online Supplementary Figure S1*). The exclusion criteria included a co-diagnosis of multiple myeloma (patients whose only myeloma defining event was serum free light chain ratio ≥100 could be included) or Waldenström's macroglobulin-

Table 1. Baseline demographic and clinical characteristics of the patients (N=40).

Characteristics	N=40
Male, N (%)	30 (75.0)
Age in years, median (range)	59 (40-77)
Amyloid light-chain type λ, N (%)	31 (77.5)
Mayo 2004 stage IIIB, N (%)	20 (50.0)
Mayo 2012 stage, N (%) I II III IV	 0 (0.0) 1 (2.5) 17 (42.5) 22 (55.0)
NYHA stage, N (%) I II III IV	 2 (5.0) 14 (35.0) 23 (57.5) 1 (2.5)
Symptom-diagnosis interval in months, median (range)	8 (2-43)
Involved organs Kidney Liver	 12 (30.0) 10 (25.0)
Number of organs involved, N (%)	2 (1-4)
Laboratory values, median (range) cTnI, μg/L NT-proBNP, ng/L IVS, mm LVEF, % 24hUP, g eGFR, mL/min/1.73 m^2 ALP, U/L* dFLC, mg/L BMPC, %	 0.17 (0.07-3.07) 7,801 (803-35,000) 15 (11-23) 56 (32-83) 0.24 (0.03-12.57) 77 (12-124) 106 (38-643) 274 (72-2,966) 5 (0-25)
FISH, N (%) t(11;14), N†=39 Gain 1q21, N†=29 Del 17p, N†=29	 14 (35.9) 4 (13.8) 2 (6.9)

*The upper limit of normal is 135 U/L. †Number of patients evaluated. 24hUP: 24-hour urine protein; ALP: alkaline phosphatase; BMPC: bone marrow plasms cell; cTnI: cardiac troponin-I; dFLC: difference between involved and uninvolved free light chain; eGFR: estimated glomerular filtration rate; FISH: fluorescence *in situ* hybridization; IVS: interventricular septum; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association.

emia; severely compromised hematologic function; and inadequate liver function or estimated glomerular filtration rate < 40 mL/min/1.73 m^2 (those with renal dysfunction due to renal involvement could be included). All patients gave written informed consent prior to inclusion in this study, which was approved by the Institutional Ethics Committee of Peking Union Medical College Hospital (HS-2414) on June 23, 2020. Hematologic and organ responses were defined according to the current validated criteria.[9-12] Patients who died before response assessment and did not have a post-baseline assessment were categorized under the no-response group. All analyses were performed based on the intention-to-treat principle.

From May 2021 to March 2022, 40 patients were included (*Online Supplementary Figure S1*). Baseline demographic and clinical characteristics are displayed in Table 1. One patient whose cardiac troponin-I was 0.07 μg/L was categorized as stage III since cardiac troponin-T was higher than 0.035 μg/L. The hematologic responses are presented in Table 2. The percentage of patients who had a hematologic VGPR or better at 3 months after treatment initiation was 67.5% (95% confidence interval [CI]: 52.3-82.7), including 47.5% (95% CI: 31.3-63.7) with CR and 20.0% (95% CI: 7.0-33.0) with VGPR, and the overall response rate was 82.5% (95% CI: 70.2-94.8). Considering the best hematologic response at any time point, the intention-to-treat estimate of the CR rate was 57.5%. Twenty-eight (70.0%) patients achieved difference between involved and uninvolved free light chain (dFLC) <10 mg/L or involved free light chain ≤20 mg/L. One patient experienced hematologic progression and discontinued treatment after eight cycles. The median time to first hematologic response was 7 days (range, 7-28 days). The median time to hematologic CR was 60 days (range, 7-200 days).

A summary of the cardiac, renal and hepatic response assessments is shown in *Online Supplementary Table S1*. The percentage who had a cardiac response at 6 months was 47.5%, including 2.5% CR, 25.0% VGPR and 20.0% partial response. Cardiac progression at 6 months was observed in four (10.0%) patients. The median time to first cardiac response was 3 months (range, 1-11 months). The percentages of patients who had a renal response and a hepatic response were 41.7% and 20.0%. The median follow-up duration was 24.0 months. As of the last follow-up, eight patients had discontinued treatment due to cardiac sudden death, and two patients had died due to cardiac sudden death several months after withdrawal. Two patients died because of heart failure exacerbation from infection. The early mortality rates (within 1 month and 3 months from treatment initiation) were 15.0% and 17.5%, respectively. The 2-year OS estimate was 69.8% (95% CI: 53.0-81.6). Treatment-related adverse events (TRAE) are listed in *Online Supplementary Table S2*. Grade ≥3 TRAE occurred in 16 (40.0%) patients. The most common grade 3 TRAE were diarrhea (10.0%). Grade 4 diarrhea was noted in one patient and improved after symptomatic treatment. Grade 3 or higher pulmonary infection were noted in three patients, including bacterial pneumonia in two patients and COVID-19 pneumonia in one patient. Grade 5 bacterial pneumonia

Table 2. Summary of overall confirmed hematologic responses (N=40).

All patients	3 months N (%)	Best hematologic response N (%)	Day 8 N (%)	1 month N (%)	6 months N (%)	12 months N (%)
CR	19 (47.5)	23 (57.5)	2 (5.0)	9 (22.5)	20 (50.0)	21 (52.5)
VGPR	8 (20.0)	8 (20.0)	9 (22.5)	15 (37.5)	5 (12.5)	4 (10.0)
CR+VGPR	27 (67.5)	31 (77.5)	11 (27.5)	24 (60.0)	25 (62.5)	25 (62.5)
PR	6 (15.0)	6 (15.0)	15 (37.5)	10 (25.0)	3 (7.5)	2 (5.0)
ORR	33 (82.5)	37 (92.5)	26 (65.0)	34 (85.0)	28 (70.0)	27 (67.5)
Mayo stage IIIA						
CR	8 (40.0)	10 (50.0)	1 (5.0)	4 (20.0)	9 (45.0)	9 (45.0)
VGPR	5 (25.0)	4 (20.0)	3 (15.0)	7 (35.0)	3 (15.0)	3 (15.0)
CR+VGPR	13 (65.0)	14 (70.0)	4 (20.0)	11 (55.0)	12 (60.0)	12 (60.0)
PR	6 (30.0)	5 (25.0)	9 (45.0)	8 (40.0)	3 (15.0)	2 (10.0)
ORR	19 (95.0)	19 (95.0)	13 (65.0)	19 (95.0)	15 (75.0)	14 (70.0)
Mayo stage IIIB						
CR	11 (55.0)	13 (65.0)	1 (5.0)	5 (25.0)	11 (55.0)	12 (60.0)
VGPR	3 (15.0)	4 (20.0)	6 (30.0)	8 (40.0)	2 (10.0)	1 (5.0)
CR+VGPR	14 (70.0)	17 (85.0)	7 (35.0)	13 (65.0)	13 (65.0)	13 (65.0)
PR	0 (0.0)	1 (5.0)	6 (30.0)	2 (10.0)	0 (0.0)	0 (0.0)
ORR	14 (70.0)	18 (90.0)	13 (65.0)	15 (75.0)	13 (65.0)	13 (65.0)

CR: complete response; ORR: overall response rate; PR: partial response; VGPR: very good partial response.

occurred in one patient, who died of infection-induced heart failure exacerbation afterward. Four patients, one patient and one patient suspended bortezomib due to diarrhea, intestinal obstruction and acute cholecystitis, respectively. One patient reduced the dose of bortezomib because of diarrhea.

The proportions of hematologic CR, VGPR or better in Mayo stage IIIB patients were comparable to those in Mayo stage IIIA patients (Table 2). Although the early mortality rate within 1 month was higher in the IIIB subgroup (25.0% and 5.0%, respectively), the percentages of cardiac response at 6 months were similar between IIIA and IIIB (45.0% and 50.0%, respectively). The 2-year OS rates were 74.3% (95% CI: 48.7-88.4) and 65.0% (95% CI: 40.3-81.5) in the IIIA and IIIB subgroups, respectively (Figure 1).

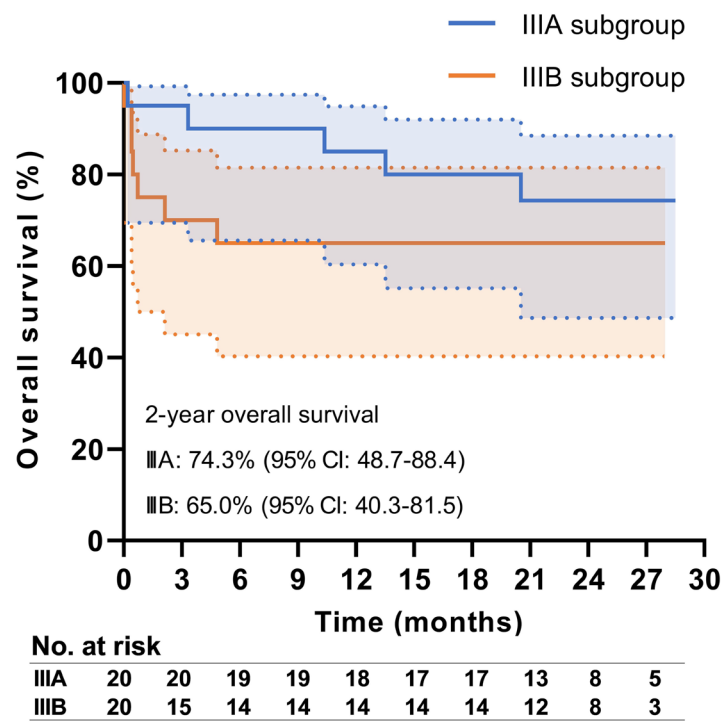

Figure 1. Kaplan-Meier graph of overall survival by Mayo 2004 stage. The blue and orange areas indicate the 95% confidence interval (CI) of overall survival.

To our knowledge, this is the first study in AL patients with stage III disease, including those with N-terminal pro-brain natriuretic peptide >8,500 ng/L, that prospectively explored the efficacy and safety of a daratumumab-based regimen. In the current study, the hematologic and cardiac responses of Dara-VD compared favorably with those reported with bortezomib-based therapy. Median OS was significantly extended even in the IIIB subgroup.[13] Along with pursuing a rapid and deep hematologic response, minimizing side effects is equally important in the management of advanced cardiac AL patients. Thus, the EMN22 study tried to explore the feasibility of daratumumab monotherapy in newly diagnosed stage IIIB patients and reported early results in 40 patients.[8] The overall hematologic response rate was 70.0% at 3 months and cardiac response rate was 27.5% at 6 months,[8] lower than the estimates in IIIB patients from our study. Their median OS was 10.3 months,[8] inferior to the prognosis in the current study. The early mortality rate within 1 month was 7.5%, lower than the estimate from our study. As far as we know, single-agent daratumumab may compromise the rapidity and depth of the hematologic response, which is strongly associated with the cardiac response and long-term survival. Before the routine application of anti-fibrillary antibodies in AL amyloidosis, our findings highlight the importance of upfront combination treatment in late-stage patients.

Given the strong anti-plasma cell effect of daratumumab combined with bortezomib, we wondered whether it was necessary to include alkylating drugs in first-line therapy. Thus, when we designed the current trial, cyclophosphamide was abandoned to reduce myelosuppression. Chakraborty *et al*. recently published a retrospective analysis of 19 IIIB patients treated with Dara-VCD front-line therapy.[14] The proportions of patients achieving ≥ VGPR at 3 months were similar.[14] Cardiac response was achieved by 56% of Chakraborty *et al*.'s patients, and their 1-year OS was 67.5%,[14] similar to the estimates in our study. The early mortality rate within 1 month was 10.5%. Grade ≥3 infections were noted in 21.1% of their patients,[14] while the percentage in our study was 15.0%. The comparable response and survival further support the advantage of the upfront combination regimen in IIIB patients. As we assumed, alkylating agents do not need to be used initially.

Of note, bortezomib-related diarrhea was prominent in this group of patients with advanced cardiac damage.[4] We did record grade 3-4 diarrhea in 12.5% of cases. Therefore, close monitoring and thorough patient education are key to avoiding volume deletion and electrolyte disturbances from diarrhea. It was noteworthy that five early cardiac deaths occurred in stage IIIB patients. One limitation of current study was that the starting dose of bortezomib was not reduced for these patients with very advanced disease. In a recently published retrospective study on IIIB patients treated with daratumumab either with or without bortezomib, the percentage of patients who experienced early mortality within the first 2 months after initiating therapy was also as high as 22%.[15] It remains uncertain whether a dose titration of bortezomib and dexamethasone could have potentially reduced arrhythmic deaths while maintaining a satisfactory impact on treatment response quality and rate in stage IIIB patients. Only a further comparative study might answer this question.

In conclusion, our trial demonstrates that the Dara-VD regimen is well tolerated and has promising efficacy even in AL patients with very advanced cardiac involvement.

Authors

Kai-ni Shen,[1*] Ya-juan Gao,[1*] Long Chang,[1] Lu Zhang,[1] Xin-xin Cao,[1] Zhuang Tian,[2] Yi-ning Wang,[3] Dao-bin Zhou[1] and Jian Li[1,4]

[1]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union

Medical College; [2]Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College; [3]Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College and [4]State Key Laboratory of Common Mechanism Research for Major Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**KNS and YJG contributed equally as first authors.*

Correspondence:
J. LI - lijian@pumch.cn

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Disclosures

No conflicts of interest to disclose.

Contributions

KNS and JL contributed to the concept and design of the study. KNS, YJG, LC, LZ, XXC, ZT, YNW, DBZ and JL collected data, KNS and YJG further contributed to data analysis and drafted the manuscript. All authors contributed to data interpretation, critically reviewed the manuscript and approved the final version.

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Data-sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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