

Daratumumab in light chain deposition disease: rapid and profound hematologic response preserves kidney function

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Key Points

- Daratumumab is effective in treated light chain deposition disease.
- Daratumumab can prevent progression of renal failure in these patients.

Introduction

Light chain deposition disease (LCDD) is a monoclonal gammopathy of clinical significance¹ that is characterized by the formation of unstructured tissue deposits of the monoclonal immunoglobulin light chain. The kidney is involved in almost all patients. Renal involvement results in proteinuria, hypertension, and microhematuria. The clonal plasma cell infiltrate is usually small (<10% in ~85% of patients).² In the absence of an effective therapy, the disease progresses to chronic kidney failure, eventually requiring renal replacement therapy.³⁻⁶

Treatment is based on regimens used in multiple myeloma and amyloid light chain (AL) amyloidosis; few studies have reported the outcome of treated patients. Currently, most patients receive bortezomib upfront, which is usually combined with cyclophosphamide and dexamethasone.^{2,7} Sayed et al reported the largest and most recent series of patients with LCDD.² Of a total of 53 subjects, 9 were treated with a bortezomib-based regimen (8 patients achieved a complete response [CR], and 1 achieved a partial response [PR]). In that study, all patients were assessed for hematologic response to therapy in accordance with the criteria proposed and validated in AL amyloidosis.⁸ The patients who obtained a good quality hematologic response to therapy (ie, CR or very good PR [VGPR]) also enjoyed an improvement in renal function.^{2,9} Profound hematologic response and improvement in renal function were also reported in small series after autologous stem cell transplant (ASCT).^{2,10-12} In particular, Cohen et al showed that hematologic response rates were similar (~90%) after ASCT and bortezomib-based regimens upfront.¹³ The outcome of relapsed and refractory LCDD patients has not been studied systematically.

Daratumumab is an anti-CD38 monoclonal antibody that is highly effective in multiple myeloma patients as a single agent¹⁴ and in combination with proteasome inhibitors¹⁵ or immunomodulatory agents.^{16,17} Daratumumab was used in previously treated patients with AL amyloidosis with encouraging results.¹⁸⁻²⁰ This agent became available in July 2017 in Italy for the treatment of relapsed/refractory multiple myeloma.

Case description

We report the outcome of 8 patients with LCDD and a baseline bone marrow plasma cell infiltrate >10% who were treated with daratumumab according to Italian Medicine Agency regulations. Briefly, all patients had a diagnosis of multiple myeloma and had received ≥1 prior line of therapy. In addition, patients who received treatment with a proteasome inhibitor and an immunomodulatory agent and had progressive disease were eligible for daratumumab monotherapy. All patients gave written informed consent for their clinical data to be used for research purposes, in accordance with the Declaration of Helsinki. All subjects were scheduled to receive IV daratumumab at the standard recommended dose for multiple myeloma: 16 mg/kg weekly for 8 weeks, followed by every other week for 8 doses, and then every 4 weeks. Five patients received daratumumab as a single agent, and 3 patients were treated with

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Table 1. Patient characteristics

ID	Age, y	Previous lines of therapy, n	Previous exposure*	BMPC at diagnosis, %	MC, type	Creatinine, mg/dL	eGFR, mL/min per 1.73 m ²	CKD stage	Proteinuria, g/24 h	dFLC, mg/L	FLC κ/λ ratio	Main side effect
1	69	5	MDex, BDex, PDex, TDex, Be-P	10	IgGκ	2.29	32	4	1.08	144	27.0	—
2	41	1	CyBorD	23	LCκ	4.03	15	4	0.77	52	2.01	—
3	74	5	MDex, BDex, LDex, PDex, Be-P	30	BJPκ	2.00	32	3	1.56	2740	139	Pneumonia
4	66	5	MDex, BDex, LDex	10	IgGκ	1.56	34	3	1.83	174	8.5	—
5	59	1	CyBorD	12	LCκ	3.84	12	5	2.83	435	16.5	Pneumonia
6	55	4	MDex, BDex, PDex	15	BJPκ	2.37	30	3	1.86	247	25.2	—
7	64	1	CyBorD	13	IgGκ	2.37	21	4	0.51	1199	78.3	—
8	30	4	MDex, BDex, TDex, PDex	10	BJPκ	3.36	23	4	1.00	88	2.5	—

—, no main side effect reported; BDex, bortezomib and dexamethasone; Be-P, bendamustine and prednisone; BJP, Bence Jones protein; BMPC, bone marrow plasma cell infiltrate; CKD, chronic kidney disease; CyBorD, cyclophosphamide, bortezomib and dexamethasone; IgG, immunoglobulin G; LC, light chain-only monoclonal protein; LDex, lenalidomide and dexamethasone; MC, monoclonal component; MDex, melphalan and dexamethasone; PDex, pomalidomide and dexamethasone; TDex, thalidomide and dexamethasone.

*Treatment regimens are reported in order of use. Patients 2, 5, and 7 received daratumumab, bortezomib, and dexamethasone.

daratumumab, bortezomib, and dexamethasone.¹⁵ The median number of infusions given was 16 (range, 8-24).

Methods

Hematologic response to therapy was assessed according to International Society of Amyloidosis criteria.^{2,8,21-23} Briefly, CR was defined as a normal free light chain (FLC) ratio and negative serum and urine immunofixation; VGPR was defined as the difference between involved and uninvolved FLCs (dFLC) <40 mg/L after therapy, and PR was defined by a decrease in dFLC ≥50%. Hematologic response and renal function data were collected after 16 infusions of daratumumab. Renal response was defined as a decrease in proteinuria >30% compared with baseline, in the absence of renal progression (decrease in the estimated glomerular filtration rate >25%), in patients with a baseline proteinuria >0.5 g per 24 hours, according to Palladini et al.²⁴

Results and discussion

Eight patients (6 males and 2 females), aged from 30 to 74 years, were included. All subjects received ≥4 consecutive months of treatment between September 2017 and September 2019. Patients' clinical characteristics are reported in Table 1. The diagnosis was based on kidney biopsy; myeloma cast nephropathy was excluded in all cases. None of the patients had extrarenal organ involvement by LCDD. All patients had baseline bone marrow plasma cell infiltrate >10%; however, none had lytic bone lesions at skeletal survey at the time of diagnosis. The median dFLC level at the time of treatment initiation was 210 mg/L (range, 52-2740), median estimated glomerular filtration rate (eGFR) was 30 mL/min per 1.73 m² (range, 12-34), and median proteinuria was 2 g per 24 hours (range, 0.5-2.8). At the time of daratumumab initiation, renal progression compared with the previous control had occurred in 4 patients. All patients were refractory to the last line of therapy. The median time from the diagnosis of LCDD to daratumumab initiation was 57 months (range, 8-107). Three patients received 5 previous regimens, 2 subjects received 4 prior lines of treatment, and 3 patients received only cyclophosphamide, bortezomib, and dexamethasone as the first-line option. All patients received

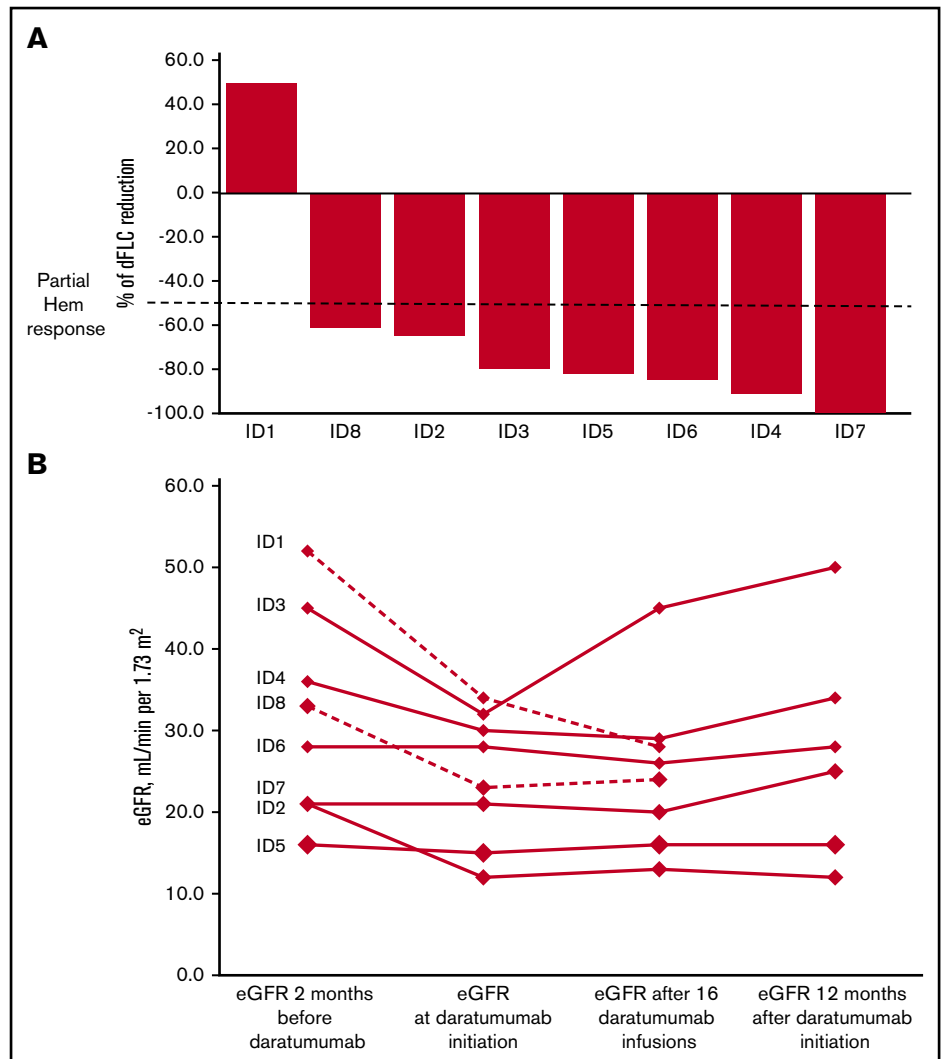
bortezomib and an alkylating agent, and 5 received an immunomodulatory drug. Four patients underwent an ASCT. Those who received only 1 previous line of treatment were treated with daratumumab, bortezomib, and dexamethasone, in accordance with Italian Medicine Agency regulations.

Treatment was generally well tolerated, and no severe infusion-related reaction was observed. Within the limit of the retrospective setting and the relatively short follow-up, no severe grade 4 adverse event was noted. Daratumumab was temporarily discontinued in 2 patients because of respiratory infections (Common Terminology Criteria for Adverse Events grade 2) that resolved without hospitalization. Changes in dFLC after 8 infusions of daratumumab are shown in Figure 1A. Response data per single patients are reported in supplemental Table 1. Seven of the 8 patients achieved at least a PR, and 4 subjects achieved a VGPR. All 7 responders are still being treated with daratumumab (1 infusion every 28 days), and the hematologic response was confirmed in all cases after a median follow-up of 20 months (range, 12-27 months) from treatment initiation.

Two patients achieved a renal response according to AL amyloidosis criteria. In both cases, a high quality hematologic response (VGPR) was reached. In the 4 patients in whom eGFR was worsening at the time of daratumumab initiation, further deterioration of renal function was prevented. eGFR remains stable in 3 patients after a median follow-up of 11 months (range, 8-15), and eGFR improved by 50%, from 30 mL/min per 1.73 m² to 45 mL/min per 1.73 m², in another patient (Figure 1B). In all of those patients, at least a PR was reached after daratumumab initiation. In our cohort, 2 patients progressed to end-stage renal disease, both ~12 months after daratumumab initiation. One of them, who had a baseline eGFR of 32 mL/min, did not respond to daratumumab. The second patient had a baseline eGFR of 22 mL/min and achieved a PR with daratumumab but experienced a further deterioration in renal dysfunction.

This is the first report on the use of daratumumab therapy in previously treated LCDD patients. This agent yielded a rapid and significant hematologic response in 7 of 8 patients with refractory

Figure 1. Response data. (A) Best dFLC change in individual patients. (B) eGFR changes during treatment.



disease. The high rate and the good quality of the hematologic response occurred in a subgroup of patients with high tumor burden. Addition of daratumumab to bortezomib overcame the resistance to this drug in 3 subjects. Response to daratumumab could prevent deterioration of renal function in 6 of 7 cases. The possible use of this drug earlier in the course of the disease, which might result in deeper and more frequent responses and prevent the onset of renal failure, deserves further investigation. Daratumumab represents a promising treatment option for relapsed and refractory LCDD patients, and larger international studies are warranted.

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Authorship

Contribution: P.M. and G.P. designed the study, evaluated patients, collected and analyzed data, and wrote the manuscript; G.M.

designed the study, evaluated patients, and critically reviewed the manuscript; M.B., P.C., A.F., R.R., M.N., R.G., L.G., and G.S. evaluated patients, collected data, and critically reviewed the manuscript; and all authors approved the final version of the manuscript.

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