Safety and Efficacy of Triplet Regimens in Newly Diagnosed Light Chain Amyloidosis

Ajai Chari, Kevin Barley, Sundar Jagannath, Keren Osman

Abstract

A retrospective review was performed of 9 patients with light chain amyloidosis who received a modified triplet regimen. We observed rapid hematologic responses in 8 of 9 patients and cardiac responses in all 4 patients with cardiac involvement.

Background: The prognosis of patients with systemic light chain (AL) amyloidosis, particularly cardiac, is poor. Treatments have been derived from multiple myeloma, but there are few studies that use triplet regimens in AL amyloidosis because of concern of greater toxicity than seen in myeloma. **Patients and Methods:** We conducted a retrospective review of patients with newly diagnosed AL amyloidosis who were initially treated with a triplet regimen. **Results:** For the 9 patients included, the median age was 64 years, and 8 were ineligible for stem cell transplantation. At least 2 organs were involved in 4 patients, including 7 with kidney and 4 with heart involvement, 2 of whom had New York Heart Association class 3 heart failure. All the patients received bortezomib, cyclophosphamide or lenalidomide/thalidomide, and dexamethasone. With a median follow-up of 13 months, 8 of 9 patients had a hematologic response, including 2 who achieved complete response, with a median time to response of 2.7 months. An organ response was seen in 7 of 9 patients, including all 4 patients with cardiac involvement. There were no deaths, and only 1 patient had progressive disease. The major toxicity observed was fluid overload and syncope, seen only in patients with heart failure, who eventually achieved a partial or complete response. **Conclusions:** Dose-attenuated triplet regimens achieved rapid hematologic responses with manageable and reversible toxicity in patients with newly diagnosed AL amyloidosis.

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Introduction

Systemic light chain (AL) amyloidosis is a clonal plasma cell dyscrasia characterized by immunoglobulin light chain deposition that resulted in end organ damage.[1] Depending on the degree of cardiac involvement, the median overall survival (OS) can range from 27.2 months, if uninvolved, to 4.1 months, if severely involved.[2] Treatment is targeted at the destruction of the plasma cell clone, and, although the approaches are the same as those used in multiple myeloma (MM), there is concern for greater toxicity in AL amyloidosis.[3-5] For example, only 20% to 25% of patients with AL amyloid are eligible for high-dose melphalan chemotherapy with autologous stem cells rescue.[6]

Similarly, bortezomib and the immunomodulatory drugs thalidomide and lenalidomide (IMiD) have been studied with or without corticosteroids in both MM and AL amyloid.[3,4,7,8] The overall response rate (ORR) for doublet regimens ranges from 41% to 83%, with <30% of patients having a cardiac response.[3-5,7,9-12] The rate of grade 3 to 4 adverse events in these studies is high, particularly when treatment was initiated with high doses of IMiDs.[4,7,9,10] Preclinical synergy between proteasome inhibitors, IMiDs, and conventional chemotherapeutics prompted clinical trials of triplet regimens with unprecedented ORR and complete response (CR) rates that ranged from 57% to 100% and 3% to 37%, respectively, in newly diagnosed MM.[9,13-28] Given these impressive outcomes and the need for a rapid and deep hematologic response in AL amyloid to achieve organ improvement, the use of appropriately dose-attenuated triplet regimens in AL amyloidosis needs to be explored.

Recently, 2 studies that combined bortezomib, cyclophosphamide, and dexamethasone (VCD) in patients with AL were published with favorable ORRs, of 81% and 94%, respectively.[29,30]

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Division of Hematology and Oncology, Mount Sinai School of Medicine, New York, NY

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Address for correspondence: Ajai Chari, MD, Hematology and Oncology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1185, New York, NY 10029
E-mail contact: ajai.chari@mountsinai.org

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Table 1 Baseline Patient Characteristics

Patient No.	Age (y)/Sex	No. Organs Involved	Organs Involved	M Spike, mg/dL	Serum PEP/IFE	Involved Light Chain, mg/L	Kappa Lambda Ratio	24-h Urine Protein, g	24-h Urine BJP, IFE, g	Serum BNP, pg/mL	NYHA Class	ECOG PS
1	57/F	3	H, K,[a] N	—	Small free lambda	232	0.08	5.13	0.359	402	3	3
2[b]	64/M	2	H, N	1.02	IgG lambda	375	0.048	0.125	—	321	2	1
3	44/F	5	H, K,[a] GI,[a] N, A	0.38	IgA lambda	37.2	0.147	6.344	Faint IgA lambda	410	3	1
4	77/M	1	K[a]	—	Lambda light chain	523	0.07	10.3	0.76	160		3
5	66/F	1	K[a]	1.49	IgG lambda	129	0.086	3.28	1.11	26		1
6[b]	76/F	1	K	—	IgA lambda	51.8	0.263	6.72	Faint IgA lambda	51		1
7	54/F	2	K,[a] L[a]	—	Undetectable	96.5	9.8	7.64	—	89		0
8	71/M	1	K[a]	0.56	IgM lambda	53	0.29	7.1	0.74	75		0
9	59/F	1	H[a]	0.42	IgA kappa	75.2	7.49	0.068	Faint IgA kappa	2155	2	1

Abbreviations: A = adrenal; BJP = Bence Jones protein; BNP = brain natriuretic peptide; ECOG PS = Eastern Cooperative Oncology Group performance status; GI = gastrointestinal; H = heart; IFE = immunofixation; Ig = immunoglobulin; K = kidney; M spike = monoclonal protein spike; N = nerves; NYHA = New York Heart Association; PEP = protein electrophoresis.
[a] Organ with amyloid present on biopsy.
[b] Patient no. 2 had amyloid present on fat pad aspiration and bone marrow biopsy; patient no. 6 had amyloid present on fat pad aspiration.

However, neither toxicities observed nor the organ responses for the 10 newly diagnosed patients in each study are available. Also, many of these patients were treated with twice weekly bortezomib, which is associated with increased toxicity, and with dexamethasone 20 to 40 mg per week, which can be challenging for cardiac patients. Most importantly, the efficacy and safety of a dose-attenuated immunomodulatory drug that contains triplet regimens has not been reported in AL amyloidosis. Here, we retrospectively review the outcome of patients newly diagnosed with AL amyloidosis who were treated with this regimen.

Patients and Methods

In this retrospective study, the patients were selected from the plasma cell disorder program at Mount Sinai School of Medicine. The study was approved by the Mount Sinai Institutional Review Board. Inclusion criteria were a biopsy-proven diagnosis of AL amyloidosis with associated end organ damage and initial treatment with a 3-drug regimen. Exclusion criterion was a diagnosis of symptomatic MM or a prior plasma cell–directed therapy; however, prior monotherapy with corticosteroids was permitted. Assessments of organ involvement and of hematologic and organ response were made on the basis of consensus criteria from the 10th International Symposium on Amyloidosis, which uses the involved free light chain (FLC) for determination of FLC response.[31] There are no consensus criteria to assess nervous system and gastrointestinal response, so response assessment was based on clinical signs and symptoms. Adverse events were graded according to the National Cancer Institute Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (version 4.0). Progression-free survival was calculated, by using Kaplan-Meyer analysis, from the date of diagnosis to the date of disease progression or death. OS was calculated from the date of diagnosis to the date of death.

Results

Patient Characteristics

Nine patients with newly diagnosed, previously untreated AL amyloidosis initiated treatment with a triplet regimen and were included in this analysis. The baseline characteristics of patients are summarized in Table 1. The median age was 64 years, and a third of the patients were men. At least 2 organs were involved in 4 (44%) patients, and renal involvement with nephrotic syndrome was present in 7 (78%) patients. There was cardiac involvement in 4 (44%) patients, 2 of whom presented with New York Heart Association class 3 heart failure. Although N-terminal probrain natriuretic peptide measurements were not available, when using brain natriuretic peptide as a surrogate, all the cardiac patients had elevated brain natriuretic peptide levels and half had elevated cardiac troponin I levels (patient nos. 1 and 9), making them Mayo Clinic stage II and III.

Treatment

The treatment regimens are summarized in Table 2. All the patients initiated therapy with bortezomib, a corticosteroid, and either an immunomodulatory agent or an alkylating agent. Most patients received bortezomib 1.3 mg/m^2 weekly for 3 consecutive weeks with a 1-week rest between cycles. Five (56%) of the 9 patients received bortezomib subcutaneously at some point during therapy. All the patients who received lenalidomide were started on 10 or 15 mg daily for 21 days, and those who received thalidomide were treated at 100 mg daily. Of note, all the patients with nephrotic range proteinuria who received IMiDs were also prescribed anticoagulation with either enoxaparin, warfarin, or aspirin. While awaiting the arrival of immunomodulatory agent delivery to patients, 6 (67%) of the 9 patients initially received at least 1 alkylator-based triplet cycle before starting the IMiD-