ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Analysis of diagnostic and therapeutic strategies in advanced cardiac light-chain amyloidosis

Inés Sayago, MD,[a] Isabel Krsnik, MD, PhD,[b] Manuel Gómez-Bueno, MD,[a] Pablo García-Pavía, MD, PhD,[a] Natalia Jaramillo, MD,[a] Clara Salas, MD, PhD,[c] Susana Mingo, MD, PhD,[a] Juan F. Oteo, MD,[a] Luis Alonso-Pulpón, MD, PhD,[a] and Javier Segovia, MD, PhD[a]

From the [a]Department of Cardiology, Advanced Heart Failure and Heart Transplantation Unit, Hospital Puerta de Hierro, Majadahonda, Madrid, Spain; [b]Department of Hematology, Hospital Puerta de Hierro, Majadahonda, Madrid, Spain; and the [c]Department of Pathology, Hospital Puerta de Hierro, Majadahonda, Madrid, Spain.

KEYWORDS:
biopsy;
bortezomib;
cardiac amyloidosis;
light-chain amyloidosis;
NT-proBNP

BACKGROUND: Prognosis of advanced cardiac light-chain amyloidosis (ACAL) is ominous. Diagnosis of ACAL is frequently preceded by several biopsies of non-clinically affected tissues, which can result in dangerous treatment delays. Combinations of alkylators and steroids have a limited role in its therapy. Definitive efficacy of bortezomib in ACAL is not widely described. In this study we analyze the diagnostic yield of biopsies and compare the effect of bortezomib with other therapeutic strategies in ACAL patients.

METHODS: This study is a retrospective analysis of 40 consecutive ACAL patients treated at our hospital (2005 to 2015). For comparison purposes, the cohort was divided into 2 groups: patients treated with bortezomib ($n = 23$) and those treated with other therapeutic approaches (non-bortezomib, $n = 8$).

RESULTS: Sensitivity of biopsies of non-clinically affected organs was 23%, as compared with 97% for affected organ biopsies ($p < 0.0001$). The need for >2 biopsies resulted in an average delay in diagnosis of 4.1 months ($p = 0.007$). Hematologic response was observed in 96% of patients in the bortezomib group compared with 25% in the non-bortezomib group (relative risk = 3.8; 95% confidence interval 1.14 to 12.75; $p = 0.0002$). Cardiac response criteria were met by 60% of patients in the bortezomib group as compared with none in the non-bortezomib group ($p = 0.005$). Survival at 6 months and 1 and 2 years for bortezomib patients was 91%, 91% and 73%, as compared with 58%, 15% and 0% for non-bortezomib patients (log rank, $p < 0.0001$), respectively.

CONCLUSION: In our experience, the sensitivity of biopsies from non-affected organs in ACAL is poor and could result in diagnostic delay. Bortezomib was associated with higher hematologic and cardiac response rates as well as survival when compared with other therapies.

J Heart Lung Transplant ▮▮▮▮;▮:▮▮▮–▮▮▮

Systemic light-chain amyloidosis (AL) is the most prevalent amyloid syndrome. It is the result of tissue accumulation of misfolded fragments of monoclonal immunoglobulin light chains usually synthesized by an underlying clonal plasma cell dyscrasia. Heart involvement occurs in 60% of AL patients and, once it appears, median survival without treatment is approximately 6 months.[1]

Diagnosis of cardiac involvement requires either demonstration of amyloid deposits in myocardial tissue or a positive biopsy in other tissues plus echocardiographic

Reprint requests: Javier Segovia, MD, PhD, Department of Cardiology, Advanced Heart Failure and Heart Transplantation Unit, Hospital Puerta de Hierro, Majadahonda, Madrid 28222, Spain. Telephone: +34-911-917-843. Fax: +34-911-917-718.

E-mail address: jsecu@telefonica.net

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2016.03.004

criteria.[2] Biopsies from non-clinically affected organs, such as abdominal fat, salivary glands or rectal sub-mucosa, are frequently performed, but their sensitivity is low and may result in delay of both diagnosis and treatment initiation.

Combinations of alkylators (melphalan or cyclophosphamide) and steroids (prednisone or dexamethasone), with or without thalidomide, achieve hematologic response (HR) rates of 65% to 75% in AL patients, and have been associated with improved overall outcomes.[3] However, these regimens have a limited role in advanced cardiac AL (ACAL).[4,5]

Combinations of heart transplantation (HTx), autologous stem cell transplantation (ASCT) and chemotherapy have yielded prolonged long-term survival in selected patients.[6] However, most ACAL patients are not candidates for ASCT or HTx because of comorbidities or multiorgan amyloid involvement. In addition, the role of HTx in ACAL is still controversial, because its results are inferior to those obtained in other cardiac diseases.[7]

Bortezomib is a proteasome inhibitor that has been used to treat multiple myeloma for more than 10 years and has shown promising results in AL.[8] HR rates when combined with dexamethasone and alkylators reach 90%, with 1-year survival rates of 76% to 98%.[4] In ACAL, cardiac response (CarR) rates of 32%, HR of 68% and 1-year survival of 57% have been described recently with these combinations.[9] These data are promising, but the absence of a control group precluded the authors from drawing definitive conclusions regarding the role of bortezomib in these patients.

We have evaluated and treated 40 consecutive patients with ACAL at our institution during the last decade. The aim of our study was 2-fold: First, we assessed the diagnostic yield of biopsies obtained from different tissues in the diagnostic work-up. Second, because more than half of our patients received bortezomib, we compared outcomes in this group with those of patients managed with other therapies.

Methods

Patients

This is a retrospective analysis of a series of 40 consecutive ACAL patients treated at our hospital from July 2005 (when bortezomib was first available in our hospital) to May 2015. The study complied with the Declaration of Helsinki and the protocol was performed with institutional review board approval. Informed consent was obtained from each patient.

The diagnosis of AL and assessment of organ involvement was based on recently published criteria.[10] Performance status was evaluated using the Eastern Cooperative Oncology Group (ECOG) score[11] and the New York Heart Association (NYHA) classification. Patient work-up included clinical evaluation and a complete laboratory assessment (full blood count, basic biochemistry, protein analysis with serum and urine immunofixation and electrophoresis and serum immunoglobulin free light chains [FLC, Freelite assay]). Bone marrow aspirate and biopsy data were obtained in 37 patients (93%) for staging purposes. Plasma cell percentage was assessed in biopsy specimens by immunochemistry after staining with anti-CD138, anti-CD56, anti-κ and anti-λ.

Tissue samples were stained with hematoxylin-eosin, and the presence of amyloid was confirmed by the characteristic birefringence with Congo red staining and tioflavine. Immunohistochemical techniques with commercially available monoclonal antibodies directed against κ- and λ-light chains were used in the differential diagnosis of amyloid deposits.

Patients were diagnosed with cardiac AL when cardiac biopsy showed amyloid or when amyloid was found in other tissues and cardiac imaging criteria were fulfilled.

Cardiac evaluation at baseline and during follow-up included a complete physical exam, 12-lead electrocardiogram, echocardiogram, magnetic resonance imaging scan and assessment of cardiac biomarkers. N-terminal fragment of B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (TnI) levels were measured by standard commercially available assays. Advanced cardiac involvement was defined as Stage III of the Mayo Clinic staging system.[12]

Treatment and response

Patients were treated with standard regimens of alkylators (melphalan or cyclophosphamide) and steroids (dexamethasone or prednisone), with or without bortezomib. Bortezomib was used in the following combinations: bortezomib-dexamethasone; bortezomib-melphalan-dexamethasone; and bortezomib-cyclophosphamide-dexamethasone (CyBorD). Bortezomib dosing was 1.3 mg/m^2 weekly, bi-weekly or every 21/28 days. A full blood count, biochemical panel with NT-proBNP and FLC were performed before each cycle. A complete cardiac evaluation with echocardiogram was done every 3 months. HTx and ASCT were considered when clinically indicated by local protocols.[13,14]

Hematologic and organ responses were evaluated in accordance with recently published guidelines.[10] A complete hematologic response (CR) was defined as having no evidence of clonal disease by electrophoresis or immunofixation in serum/urine and normal serum FLC levels and ratio. Very good partial response (VGPR) was defined by a post-treatment difference between the involved and uninvolved FLC serum levels of <40 mg/liter and partial response (PR) by a 50% decrease in the involved FLC. CarR required one of the following: 30% reduction of NT-proBNP; 2-mm reduction in interventricular septum thickness; or improvement in left ventricular ejection fraction (LVEF) by 10%.[10]

Survival was calculated from the date of diagnosis until the date of last follow-up, death or HTx. We compared the outcomes of patients treated with bortezomib with those who received other therapeutic regimens. Nine patients were excluded from HR analysis due to survival of <1 month from diagnosis. Five patients who underwent HTx were excluded when CarR was analyzed.

Statistical analysis

Categorical data are expressed as percentages and were compared using the chi-square test or Fisher's exact test. Mean and standard deviation are presented for normally distributed variables and median and range for non-normally distributed ones. For statistical analysis, Student's *t*-test and Mann-Whitney non-parametric test were used in 2-group comparisons.

A univariate screening of baseline variables at enrollment was initially performed to explore the association with the occurrence of the composite event "cardiac death or HTx." The proportional hazards assumption was tested using standard log-log plots. Each variable was initially assessed with univariate analyses as a categorical variable. Hazard ratio and 95% confidence interval (CI) were estimated for each variable. Multivariate analyses of variables