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Efficacy of Chemotherapy for Light-Chain Amyloidosis in Patients Presenting With Symptomatic Heart Failure

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ABSTRACT

BACKGROUND Light-chain amyloidosis (AL) with cardiac involvement carries a poor prognosis; median untreated survival is <6 months. Three-drug therapy with bortezomib, dexamethasone, and an alkylating agent (BDex+AA) is associated with improved biomarker response rates in AL amyloidosis.

OBJECTIVES This study sought to evaluate the effect of BDex+AA as a first-line treatment strategy on mortality in patients with symptomatic heart failure from AL cardiac amyloidosis.

METHODS Patients newly diagnosed with symptomatic New York Heart Association (NYHA) functional class ≥II heart failure due to AL amyloidosis were retrospectively studied. Initial treatment strategy was adjudicated and propensity score analysis was used to adjust for the nonrandomized allocation of treatments. Survival was assessed using a Cox proportional hazards model after adjusting for the propensity score for receiving treatment, age, NYHA functional class, and ejection fraction.

RESULTS Among 106 treated patients (age 64.6 ± 11.3 years, 63% male, 76% lambda subtype), 40 received the 3-drug regimen and 66 received other regimens. Mortality was 65% overall, 48% in the BDex+AA cohort (median survival time 821 days), and 76% in patients who received other regimens (median survival time 223 days). Initial treatment with BDex+AA was associated with decreased mortality after multivariable adjustment (hazard ratio: 0.209; 95% confidence interval: 0.069 to 0.636; p = 0.006). This association remained after further adjustment for components of the Mayo Stage.

CONCLUSIONS Use of BDex+AA in the treatment of AL amyloidosis in patients presenting with symptomatic heart failure is associated with improved survival after adjusting for clinical variables. (J Am Coll Cardiol 2016;67:2941–8)

Amyloidosis is a disease in which misfolded proteins aggregate into fibrils, deposit in the extracellular matrix, and result in organ dysfunction (1). Cardiac involvement almost exclusively develops from the deposition of either transthyretin or immunoglobulin light chains (AL), leading to a restrictive cardiomyopathy. AL amyloidosis, a disease of clonal plasma cells, can be rapidly fatal, with a median survival of 6 months without treatment if cardiac involvement is diagnosed (2). Heart failure at presentation carries the worst prognosis compared with other manifestations (3), yet heart failure symptom assessment is underrepresented in current analyses of treatment effects.

Therapeutic regimens for AL amyloidosis have evolved over time. The combination of prednisone and melphalan, an alkylating agent, was first established in 1997 and conferred improved survival compared with colchicine (3). High-dose dexamethasone was then substituted for prednisone due to a

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ABBREVIATIONS AND ACRONYMS

AL = immunoglobulin light chain

BDex+AA = bortezomib, dexamethasone, and alkylating agent

CI = confidence interval

dFLC = free light-chain difference

LV = left ventricle/ventricular

LVAD = left ventricular assist device

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

OR = odds ratio

more rapid response rate (4). Bortezomib, the first therapeutic proteasome inhibitor, is very effective against plasma cells and has shown promising results in addition to background therapy in AL amyloidosis. Bortezomib, when added to melphalan and dexamethasone, provided a higher response rate, but no change in mortality, in a matched case-control study. However, there was a survival advantage in lower-risk patients (5). A similar effect on hematologic response was noted when bortezomib was compared with thalidomide in the setting of background therapy with cyclophosphamide (another alkylating agent) and dexamethasone (6). Bortezomib, when added to an alkylating agent and dexamethasone (BDex+AA), is thought to work synergistically in arresting the life cycle of clonal plasma cells (7).

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These studies included a varied number of patients with cardiac involvement as defined by the Mayo stage, which is based upon the biomarkers troponin T, N-terminal of the prohormone of brain natriuretic peptide (NT-proBNP), and the free light-chain burden (8). However, few have assessed the presence or severity of heart failure symptoms. Although BDex+AA has emerged as the treatment of choice in all-comers with AL amyloidosis due to improved biomarker response rates, there are no direct mortality data confirming benefit in patients with symptomatic heart failure. We sought to evaluate the effect of BDex+AA as a first-line treatment strategy on mortality in patients presenting with symptomatic heart failure from AL cardiac amyloidosis.

METHODS

STUDY POPULATION. Consecutive patients seen at our institution from 2004 to 2015 with confirmed AL cardiac amyloidosis were reviewed and included for analysis. All patients were newly diagnosed, and had New York Heart Association (NYHA) functional class II to IV heart failure symptoms at presentation. Patients who had received immunosuppression previously (i.e., for multiple myeloma) were excluded. Patients who did not undergo treatment were included in Kaplan-Meier analysis as a separate group, but not included in subsequent modeling.

DIAGNOSTIC CRITERIA. A diagnosis of AL amyloidosis was based on clinical presentation and the assessment of serum immunoglobulin free light chains and immunofixation. Histological diagnosis was achieved with endomyocardial and/or bone marrow biopsy staining with Congo Red or Thioflavin S, and confirmed with immunohistochemistry and/or mass spectrometry. Patients who did not undergo endomyocardial biopsy were diagnosed with cardiac involvement on the basis of advanced imaging criteria in the setting of known extracardiac amyloidosis. Cardiac magnetic resonance imaging was considered positive for amyloid cardiomyopathy if there were morphological and structural abnormalities consistent with the diagnosis, for example, wall thickening of the left (LV) or right ventricle or interatrial septum and biatrial enlargement, coupled with abnormal gadolinium kinetics and diffuse subendocardial or transmural delayed gadolinium enhancement. Echocardiographic criteria were structural and functional changes consistent with amyloid infiltration: anteroseptal or posterior wall thickness >12 mm without another cause of LV hypertrophy, biatrial enlargement, low tissue Doppler velocities, and short deceleration time, as well as an apical sparing pattern of peak systolic longitudinal strain (9).

Extracardiac involvement was evaluated in 5 organs as defined by the most recent consensus statement (10), and required histological, laboratory, or symptomatic diagnosis. In the absence of a histological diagnosis, liver involvement was diagnosed if alkaline phosphatase was >1.5 times the upper limit of normal, renal involvement if 24-h urine protein was ≥0.5 g/day, nerve involvement if symmetric extremity sensorimotor peripheral neuropathy or autonomic disorder were present, and soft tissue involvement if tongue enlargement, arthropathy, claudication, skin changes, myopathy, or carpal tunnel syndrome attributed to amyloidosis were present. Patients with pre-existing organ dysfunction were not considered to have organ involvement due to amyloidosis. Lung and gastrointestinal involvement were only diagnosed histologically.

MEASUREMENT TECHNIQUES. All patients underwent comprehensive evaluation including clinical, laboratory, electrocardiographic, and echocardiographic measurements. Electronic medical records were retrospectively reviewed, and data were adjudicated at the time of treatment initiation. Free light-chain burden was quantified using the serum immunoglobulin-free light-chain difference (dFLC), defined as the level of the affected minus the unaffected light chains. Multiple myeloma was defined as clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma along with a myeloma defining event using CRAB (hypercalcemia, renal failure, anemia and bone lesions)