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Outcomes from Autologous Hematopoietic Cell Transplantation versus Chemotherapy Alone for the Management of Light Chain Amyloidosis

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A B S T R A C T

Light chain amyloidosis (AL) results in tissue deposition of misfolded proteins, causing organ dysfunction. In an era of modern therapies, such as bortezomib, reassessment of the benefit of autologous hematopoietic cell transplantation (AHCT) should be considered. In this study, we compared outcomes between patients with AL receiving chemotherapy alone (CT) and those undergoing AHCT. Seventy-four patients with AL were analyzed retrospectively. Two cohorts of patients were studied, those receiving CT (n = 31) and those undergoing AHCT (n = 43). Of the 43 patients in the AHCT cohort, 29 received induction chemotherapy before AHCT, whereas 14 proceeded straight to AHCT without induction therapy. Compared with the CT cohort, patients in the AHCT cohort were younger and had higher ejection fractions, lower brain natriuretic peptide levels, and more severe proteinuria. The majority (87%) of patients in the CT cohort received bortezomib-based treatment. Transplantation-related mortality (TRM) was 7%. Patients receiving AHCT were more likely to achieve complete or very good partial response ($P = .048$). The median progression-free survival (PFS) and overall survival (OS) were superior in the AHCT cohort (not reached versus 9 months; $P < .01$ and 74 months versus 8 months; $P = .03$, respectively). Multivariable analysis demonstrated that improved PFS (hazard ratio, 3.86; 95% confidence interval [CI] 1.3 to 11.5; $P = .02$) and OS (hazard ratio, 5.6; 95% CI, 1.9 to 16; $P < .001$) were associated with use of AHCT compared with CT. Patients in the AHCT cohort had deeper and longer durations of response, with superior PFS and OS, compared with those in the CT cohort. Despite the limitations of this study, AHCT should be considered for eligible patients with AL at experienced transplantation centers that can offer this therapy with a low risk of TRM.

INTRODUCTION

Light-chain (AL) amyloidosis is a monoclonal plasma cell disorder that can result in multiorgan dysfunction from amyloid fibril deposition [1]. Amyloid fibrils are misfolded immunoglobulin light chains produced from plasma cell clones [2]. Common sites of involvement include the heart, kidney, gastrointestinal tract, and peripheral and autonomic nervous systems [3].

Management of AL amyloidosis involves optimal medical management of end-organ damage along with therapy to target the plasma cells producing amyloid fibrils [4]. Standard chemotherapeutic treatment strategies include the use of chemotherapy alone, induction chemotherapy followed by autologous hematopoietic cell transplantation (AHCT), and upfront AHCT without induction chemotherapy. Historically, chemotherapy was provided with melphalan-based regimens; however, more recently, bortezomib-based therapies have been used [1,2,5,6].

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The routine use of AHCT was previously limited by high transplantation-related mortality (TRM); however, in recent years, TRM has decreased to 3% to 5% as a result of better patient selection and improved supportive care measures [3,6]. Although both AHCT and chemotherapy alone have independently demonstrated improvement in end-organ damage and hematologic response (HR), whether one treatment strategy is superior to the other has remained unclear [2,7-9]. Our primary objective in this study was to compare survival outcomes in patients with AL amyloidosis undergoing AHCT as part of their management and patients receiving chemotherapy alone without the use of AHCT.

METHODS

Patients

We report a retrospective analysis of 74 consecutive patients who received care at the Vanderbilt Amyloid Multidisciplinary Program between 2003 and 2015. AL subtype was confirmed by immunohistochemistry or laser microdissection-tandem mass spectrometry in all cases. Assessment of HR, organ involvement, organ response, and progression were based on consensus criteria [7,10]. Patients receiving fewer than 2 cycles of chemotherapy were excluded. This parameter was selected to minimize the impact of patients with advanced amyloid AL intolerant to chemotherapy and patients who succumbed to early cardiac death. Patients with concurrent multiple myeloma, defined by myeloma-attributed end-organ damage, such as hypercalcemia or bone lytic lesions, were excluded. To mitigate age bias between the 2 cohorts, only patients up to age 72 (the upper age for undergoing AHCT in this study) were permitted in the CT cohort. Hematologic and organ responses were assessed every 3 to 4 months after initiation of treatment. This study was approved by the Vanderbilt University Medical Center's Institutional Review Board.

Treatments

Two cohorts of patients were studied: those receiving systemic chemotherapy alone (designated the CT cohort; n = 31) and those who underwent AHCT (the AHCT cohort; n = 43). In our program, patients with AL with a Karnofsky Performance Status (KPS) score of ≤70%; 3 or more organs significantly affected; advanced cardiac involvement based on published guidelines (eg, New York Heart Association [NYHA] functional class ≥III); creatinine clearance ≤30 mL/min; significant effusions; or hypotension (systolic blood pressure <90 mmHg) are considered ineligible for transplantation [10,11]. Patients with a bone marrow clonal plasma cell burden <10% and no evidence of significant AL amyloid cardiac involvement (as determined by cardio-oncologic evaluation, brain natriuretic peptide [BNP] and troponin I measurements, electrocardiography, transthoracic echocardiography, and cardiac magnetic resonance imaging or endomyocardial biopsy in select cases) were permitted to proceed directly to AHCT without induction chemotherapy.

Cardiac Stage, Hematologic and Organ Response, and Progression

A complete HR (CR) was defined as negative serum and urine immunofixation, as well as normal free light chain levels and ratio. A very good partial response (VGPR) was defined as a decrease in the difference between involved and uninvolved free light chain levels to <40 mg/L. A partial response (PR) required a >50% reduction in the difference between involved and uninvolved free light chain levels. Progression (PD) was defined as going from CR to any detectable M protein or abnormal light chain ratio, a progression from PR with either a 50% increase in serum M protein to >0.5 g/dL, a 50% increase in urine M protein to >200 mg/day, or a free light chain increase of 50% to >100 mg/L [10].

Modified cardiac biomarker staging was defined by elevated BNP (>100 pg/mL) and troponin I (>0.1 ng/mL) concentrations. Stage I was defined as no elevation; stage II, as elevation of either BNP or troponin I; and stage III, as elevation of both markers [12]. To determine cardiac response, NT-proBNP was converted to BNP by a factor of 3.5:1. Cardiac response was defined as a decrease of > 30% and 85 pg/mL in BNP (with minimum baseline 185 pg/mL) or a decrease of ≥2 NYHA classes in patients designated as NYHA class 3 or 4 at baseline. Cardiac progression was defined as a >30% and 85 pg/mL increase in BNP, a ≥33% increase in troponin I, or a ≥10% decrease in ejection fraction [13,14].

Renal response was defined as a 50% decrease (at least 0.5 g/day) in 24-hour urine protein in patients who had >0.5 g/day of urine protein at baseline. Creatinine and creatinine clearance could not increase by 25% over baseline. Renal progression was defined as a 50% increase (at least 1 g/day) of 24-hour urine protein to >1 g/day or as a 25% increase in serum creatinine or creatinine clearance [10].

Outcome Measures

The primary study outcome was overall survival (OS), defined as the time from diagnosis until death from any cause or censored at the date of the last follow-up for surviving patients. Secondary outcomes included organ responses and progression-free survival (PFS). All time-to-event endpoints were measured from the beginning of treatment. Progression events were defined as death, disease progression or relapse, worsening organ function requiring a change in treatment, or initiation of second-line chemotherapy. In patients who proceeded to AHCT, this change in treatment was not censored, because this was a planned event. Transplantation-related mortality (TRM) was defined as mortality due to any cause other than disease progression within 100 days of transplantation.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Wilcoxon rank-sum test. Probabilities of PFS and OS were calculated using the Kaplan–Meier estimator. The log-rank test was performed to calculate the 95% confidence intervals [CIs] for survival probabilities. Cox-proportional hazard model was used to evaluate the effect of prognostic factors on survival outcomes and disease progression.

The primary objective of this study was to compare survival outcomes in patients undergoing AHCT and patients receiving CT alone. Other variables considered included age (<60 versus ≥60 years), 24-hour urine protein (<3.5 versus ≥3.5 g/24 hours), and modified cardiac stage (stage III versus stage I or II). A backward elimination model selection procedure was used to identify statistically significant covariates to be added into the model. All variables met the proportional hazards assumption. The cumulative incidence of relapse was calculated from the time of treatment initiation to the date of the first disease progression or relapse. A statistical significance of $\alpha = 0.05$ was applied throughout. Analyses were performed using R version 2.3.1 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Patients

Patient characteristics are summarized in Table 1. The median patient age was 61 years. The AHCT cohort was younger than the CT cohort. Although the median BNP was higher and the median EF was lower in the CT cohort, there was no statistically significant difference in modified cardiac stage or NYHA class between the 2 cohorts. Median 24-hour urine protein concentration was higher in the AHCT group. Renal involvement was more common in the AHCT group (88% [n = 35] versus 59% [n = 16]).

Outcomes of the CT Cohort

The treatments received by patients in the 2 cohorts are presented in Supplemental Figure S1. The majority of the 31 patients in the CT cohort received bortezomib-based treatment (n = 30, 97%); 1 patient (3%) received melphalan-based therapy. The median number of treatment cycles was 4. Nine patients received maintenance chemotherapy with bortezomib (n = 5) or lenalidomide (n = 4). Seventeen patients (55%) achieved an HR, including 5 (17%) with CR, 6 (20%) with VGPR, and 6 with (20%) PR (Table 2). Fourteen patients (45%) had at least one organ response (Table 2). Of the 24 patients with cardiac involvement, 10 (42%) achieved a cardiac response, while 4 of the 16 (25%) patients with renal involvement achieved a renal response. Two of the 14 (14%) patients with both cardiac and renal involvement had a response to both. The median duration of response was 7 months. The median PFS was 9 months while the median OS was 8 months. Seventeen patients (55%) in the CT cohort died (Table 3). The most frequent cause of death was progressive disease (n = 12; 71%). Two patients (12%) died from cardiac arrest, and 1 patient each died from respiratory failure, stroke, and infection.