Autologous Stem Cell Transplantation in Patients With Primary Systemic Amyloidosis: Experience of a Tertiary Hospital

M.A. Domínguez-Muñoz*, C. Calderón-Cabrera, M.L. Martino-Galiana, and J. Martín-Sánchez

Department of Hematology, Instituto de Biomedicina de Sevilla (IBIS) Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain

ABSTRACT

Background. Systemic immunoglobulin light-chain (AL) amyloidosis is a plasma cell dyscrasia that results from the deposition of insoluble fragments of immunoglobulin light or heavy chains. The subsequent disruption of organ function resulting from the extracellular deposition of these fragments ultimately leads to death. The median overall survival (OS) of patients ranges from 12 and 18 months down to 5 months in patients with cardiac involvement. Autologous hematopoietic stem cell transplantation (ASCT) is a treatment modality that achieves good response. The affected solid organ transplant (SOT) could improve performance status and have a favorable impact on survival.

Methods. Retrospective analysis of 11 AL amyloidosis patients who received ASCT from 2005 to 2013, 2 of them also underwent SOT.

Results. The 5-year OS depending on the number of organs involved (1 vs $\geq$2) was 100% versus 60% ($P = .13$). With a median follow-up of 4.8 years (range, 1.6–8), 81% of patients are alive maintaining complete hematologic response (n = 6) and very good partial response (n = 3). The 5-year progression-free survival was 80% (range, 42%–94%). Two patients underwent cardiac and renal transplantation as a bridge to ASTC. None of the double transplant patients has died.

Conclusion. ASCT is an effective treatment option in patients with AL amyloidosis. In those with advanced single organ damage, SOT should be considered to improve the clinical outcome.

PRIMARY SYSTEMIC LIGHT CHAIN (AL) amyloidosis is a plasma cell dyscrasia characterized by the production of monoclonal light chain fragments, usually of lambda isotype (3 to 1 ratio), which constitutes amorphous extracellular deposits in kidney, heart, liver, or peripheral nerves [1] causing damage and organ dysfunction.

It is an uncommon disease, and age of onset is around 65 years with an annual incidence of 0.9 new cases per 100,000 population [2]. Asthenia and weight loss are the most common symptoms, the kidney being the most frequently affected organ (70%–80%), followed by the heart (50%–60%). Heart failure is present in 15%–20% of cases at diagnosis, and may be associated with arrhythmias and syncope. Patients with AL amyloidosis who present severe heart failure owing to cardiac amyloidosis have a particularly poor prognosis, with a median overall survival (OS) of only 6 months and 100% of mortality 2 years [3–5]. Other frequent manifestations are hepatic infiltration, carpal tunnel syndrome (both around 25%) [3], gastrointestinal disorders (diarrhea), macroglosia (10%), increase of submandibular structures, voice hoarseness, mandibular intermittent claudication and purpura, particularly in upper eyelids ("raccoon eyes"; 15%). Median survival for untreated patients after diagnosis is 12 months and <5–6 months for those with cardiomyopathy [1,3].

Classically, melphalan and corticosteroids (prednisone or dexamethasone) have been used for AL amyloidosis with an overall response rate of 20%, increasing to 40% in those who had nephrotic syndrome without renal failure or heart disease [1]. In patients not eligible for autologous hematopoietic

*Address correspondence to M. Angeles Domínguez-Muñoz, Department of Hematology, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS)/CSIC/Universidad de Sevilla, Sevilla, Spain. E-mail: madomu86@hotmail.com

360 Park Avenue South, New York, NY 10010-1710

0041-1345/15
http://dx.doi.org/10.1016/j.transproceed.2015.09.052

stem cell transplantation (ASCT), the association of melphalan and dexamethasone is capable of inducing 67% of hematologic responses with 33% complete response (CR) and 48% of organic responses, with a median progression-free survival of 3.8 years and median OS around of 5 years [6]. The most promising treatment for patients under 65 years is high-dose melphalan (200 mg/m^2) followed by ASCT [7]. Cardiac involvement stage is the main predictor of survival, and hematologic response of organic response. The main limitation of this treatment is the high transplant-related mortality if used in unselected patients or performed in centers with little experience (≤30%–40% in some series).

In recent years, thanks to careful patient selection and multidisciplinary management, transplant-related mortality has decreased to an acceptable 5%–10% [8]. Eligibility criteria for ASCT with high-dose melphalan are highly variable. In general, ASCT is ruled out in patients >70 years old, those with an Eastern Cooperative Oncology Group status of >2, advanced cardiac involvement, severe dysautonomic neuropathy (usually associated with systolic blood pressure <90 mmHg) and, in some cases, lung (carbon monoxide diffusing capacity of <50%) and renal dysfunction [9]. Reducing the dose of melphalan (140 mg/m^2) in patients with higher risk may extend this treatment option to more patients, even at the cost of reducing its effectiveness. However, only one-quarter of patients diagnosed with AL will be candidates for transplantation.

The number of organs involved, clinical cardiac dysfunction, or elevation of cardiac biomarkers (troponin-T and N-terminal brain natriuretic peptide), pretransplant serum free light chain levels and ratio, and elevated serum uric acid are predictors for clinical outcome of ASCT, with number of affected organs and cardiac dysfunction being by far the dominant predictors with or without transplantation [10,11].

Solid organ transplant (SOT) can improve basal performance status and organ function in selected patients, thus increasing the number of patients eligible for ASCT and ultimately reducing mortality.

PATIENTS AND METHODS

Between March 2005 and February 2013, 11 consecutive patients with AL were evaluated at the Department of Hematology of Hospital Universitario Virgen del Rocío. Clinical and biochemical data were collected and descriptive statistics were carried out. Kaplan–Meier methods were used to estimate OS and progression-free survival. $P < .05$ was considered significant. Results were expressed as absolute numbers and percentages.

ASCT was performed as first line or consolidation therapy after ≥1 treatment lines. Two patients who had single organ involvement underwent SOT before ASCT; 1 patient required kidney transplantation and another patient heart transplantation. SOT was performed to improve baseline clinical status and try to reduce ASCT transplant-related mortality. In both patients, no other was organ affected.

The clinical characteristics of the study group are presented in Table 1. AL amyloidosis was confirmed with a tissue biopsy in all patients. Kidney was the most biopsied organ in 72%. λ-Light chain (45.5%) and κ-light chain (54.4%) were found in different tissue

Table 1. Clinical Characteristics of the Study Group

Variable	Value
Patient, n	11
Sex, n (%)	
Male	4 (36.4)
Female	7 (63.6)
Age (y), median (range)	53 (45–64)
Light chain isotype AL, n (%)	
AL IgK	6 (54.4)
AL Igλ	5 (45.5)
Diagnostic biopsy, n (%)	
Kidney	8 (72.7)
Trachea	1 (9.1)
Bone marrow	1 (9.1)
Abdominal fat	1 (9.1)
No. of organs involved, n (%)	
1	
Heart	1 (9.1)
Kidney	5 (45.5)
2	
Heart and lung	1 (9.1)
≥3	4 (36.3)
ECOG, n (%)	
0	8 (72.7)
>1	3 (27.3)
Evaluation of response pre-ASCT, n (%)	
CR	3 (27.6)
<CR	7 (63.4)
VGPR	3
PR	2
SD	2
First line of treatment	1 (9)
Dose of melphalan (mg/m^2), n (%)	
140	7 (63.7)
200	4 (36.3)
Median day 1 × 10e^9/L leukocytes	12 (9–14)
Median day >0.5 × 10e^9/L neutrophil	13 (10–15)
Median day >50 × 10e^9/L platelet	13 (9–15)
Solid organ transplant, n (%)	2 (18.2)
Heart	1
Kidney	1
Complication, n (%)	
Mucositis	9 (81.8)
I-II	5 (55.6)
III-IV	4 (45.4)
Infections	9 (81.8)
Not document microorganisms	5 (66.7)
Bacteremia (*E coli*)	4 (36.4)
Sepsis	1 (11.1)
Diarrhea	4 (36.4)
Hyperemesis	3 (27.2)
Relapsed	3 (72.7)
Currently situation hematologic	
CR	6 (66.6)
VGPR	3 (33.3)
Death, n (%)	2 (18.2)
Rhythm disorders	2 (100)

Abbreviations: AL, immunoglobulin light-chain; ASCT, autologous stem cell transplantation; CR, complete response; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; PR, partial response; SD, stable disease; VGPR, very good partial response.