Biol Blood Marrow Transplant 21 (2015) 1413–1417

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Outcome of Patients with Immunoglobulin Light-Chain Amyloidosis with Lung, Liver, Gastrointestinal, Neurologic, and Soft Tissue Involvement after Autologous Hematopoietic Stem Cell Transplantation

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Article history:
Received 13 November 2014
Accepted 30 March 2015

Key words:
Amyloidosis
Autologous hematopoietic stem cell transplantation
Response
Survival

A B S T R A C T

There is limited information on the outcome when organs other than heart or kidneys are involved by immunoglobulin light-chain amyloidosis (AL). We report the outcome of 53 patients with AL with gastrointestinal (GI), peripheral nerve (PN), liver, lung, or soft-tissue involvement, who underwent high-dose chemotherapy and autologous hematopoietic stem cell transplantation (auto-HCT) at our institution between 1997 and 2013. The median age at auto-HCT was 56 years (range, 35 to 74). One, 2, 3, or 4 organs were involved in 43%, 22%, 28%, and 4% of patients, respectively. Concurrent cardiac, renal, or both were involved in 24 (45%) patients. Forty-six patients received induction therapy before auto-HCT. The 100-day and 1-year treatment-related mortality (TRM) were 3.8% (n = 2) and 7.5% (n = 4), respectively. Forty-one (80%) patients achieved a hematologic response. Organ response at 1 year after auto-HCT was seen in 23 (57%) of the 40 evaluable patients. With a median follow-up of 24 months, the median progression-free survival and overall survival (OS) were 36 and 73 months, respectively. Auto-HCT was associated with a low TRM, durable organ responses, and a median OS of > 6 years in selected patients with AL and GI, PN, liver, lung, or soft-tissue involvement.

INTRODUCTION

Immunoglobulin light-chain systemic amyloidosis (AL) is a monoclonal plasma cell disorder characterized by the deposition of misfolded immunoglobulin free light chains as amyloid fibrils [1]. These free light chains are secreted by the clonal plasma cells and accumulate in multiple organs, causing organ dysfunction. The aim of therapy in AL is to reduce the production of misfolded light chains and preserve the function of involved organs. The treatment of AL is patterned after the treatment of multiple myeloma, another clonal plasma cell disorder. The treatment include the use of conventional cytotoxic chemotherapy agents, such as melphalan and cyclophosphamide, in standard doses [2,3]; immunomodulatory agents (IMiD), including thalidomide [4] and lenalidomide [5]; the proteasome inhibitor (PI) bortezomib [6] in combination with corticosteroids; and high-dose melphalan, followed by autologous hematopoietic stem cell transplantation (auto-HCT). Auto-HCT has been associated with longer survival in selected patients when compared with conventional chemotherapy agents [7-10] and is considered an effective treatment strategy that has been associated with hematologic response and an improvement in organ function [8], quality of life, and survival [11]. However, in the only phase 3 randomized trial, published by Jaccard et al., the outcome with high-dose melphalan plus auto-HCT was not superior to standard-dose melphalan plus dexamethasone [12]. This trial was

Financial disclosure: See Acknowledgments on page 1417.

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http://dx.doi.org/10.1016/j.bbmt.2015.03.025
1083-8791/

criticized because of the high treatment-related mortality (TRM) rate (24%) in the high-dose melphalan group, a rate that was more than twice the rate in centers performing auto-HCT for AL. That study was also notable for the inclusion of patients with more than 3 involved organs, a suboptimal dose of high-dose melphalan in 10 of 37 patients, and the inclusion of transplantation centers that perform 1 or fewer auto-HCT for AL in a year. Previous reports on the outcome of high-dose therapy and auto-HCT in AL have primarily focused on patients with cardiac or renal involvement [13,14]. Limited data are available on the role of auto-HCT when organs other than heart and kidneys are involved by AL. In this study, we evaluated the role of high-dose melphalan followed by auto-HCT in patients with gastrointestinal tract (GI), peripheral nerves (PN), liver, lung, or soft-tissue involvement by AL.

MATERIALS AND METHODS

Patients and Diagnosis

Diagnosis of AL was established by Congo red staining for amyloid fibrils with concomitant demonstration of plasma cell clonality by serum free light chain (FLC) studies, serum immunofixation electrophoresis, and bone marrow biopsy and immunohistochemistry (CD138, kappa or lambda FLC predominance), according to the criteria established at the 10th International Symposium on Amyloid and Amyloidosis [15,16]. In selected cases, FLC origin of amyloid fibrils was confirmed by mass spectrometry or electron miscroscopy.

Involvement of individual organs (GI, PN, liver, lung, or soft tissue) by AL was also established according to the criteria established at the 10th International Symposium on Amyloid and Amyloidosis [15]. Patients with GI involvement had endoscopic evaluation and biopsies. Patients with liver involvement were evaluated by liver function tests; imaging studies included computed tomography (CT) scans and ultrasound, and liver biopsy when feasible. Patients with lung and soft-tissue involvement were evaluated by imaging studies, including CT scan and biopsy of the involved organ, when feasible. Patients with PN involvement were evaluated by electromyography (EMG), nerve conduction studies (NCS), and sural nerve biopsy (2 patients) to confirm the diagnosis. All patients underwent auto-HCT between 1997 and 2013 at the University of Texas MD Anderson Cancer Center.

Auto-HCT

The choice of preparative regimen was based on the patient's performance status and the treating physician's preference. Patients received high-dose melphalan at 200 mg/m^2 or 140 mg/m^2 at the treating physician's discretion.

Hematologic and Organ Response Assessment

All patients underwent clinical, laboratory, and radiological evaluation at baseline and at 100 days and 1 year post auto-HCT. *Hematologic response* (HR) was defined according to the International Myeloma Working Group criteria [17]. Organ involvement and responses were defined by the criteria established at the 10th International Symposium on Amyloid and Amyloidosis [15].

Statistical Analysis

The primary endpoint of this study was to assess the hematologic and organ response after auto-HCT. *TRM* was defined as death due to any cause other than relapse of AL within 100 days or 1 year after auto-HCT. *Overall survival* (OS) was defined as time from auto-HCT to death or last follow-up. *Progression-free survival* (PFS) was defined as time from auto-HCT to disease progression, death, or the last follow-up. Survival was estimated by using the Kaplan-Meier method. Fisher's exact test and chi-square test were used for analyzing the differences between categorical variables. The associations of multiple factors on OS were evaluated using the Cox proportional hazards model. All P values were 2 tailed, and we accepted $P \leq .05$ as significant. All statistical analyses were performed using STATA (Stata Statistical Software: Release 12. StataCorp LP, College Station, TX).

RESULTS

Patients

We identified 53 patients with AL who met the inclusion criteria for these analyses. Patient characteristics are summarized in Table 1. The median follow-up among surviving patients was 25 months (range, 3 to 144).

Hematologic Involvement at Diagnosis

Thirty-two (60%) patients had lambda FLC subtype and 19 (36%) patients had κappa FLC subtype of AL. Serum FLC were available in 42 (79%) patients before auto-HCT. The median difference in involved and uninvolved FLC (dFLC) was 59 (range, 0 to 1237) before transplantation. As shown in Table 1, 21 (39%) patients had a dFLC of $<$ 18, whereas 21 (39%) patients had a dFLC of $\geq$ 18. Median plasma cell percent in the bone marrow at diagnosis was 13% (range, 1 to 100).

Organ Involvement at Diagnosis

Organ involvement was defined according to the International Society of Amyloidosis criteria [15]. Clinical features of organ involvement are summarized in Table 2. Patients with GI involvement presented with abdominal mass, bleeding, diarrhea, motility disturbance, nausea, or weight loss. Upper or lower GI endoscopy was performed to confirm the diagnosis of AL. A limited number of patients also underwent barium studies to evaluate the GI tract. Patients with neurologic involvement had symmetrical peripheral neuropathy or autonomic neuropathy. In selected patients, EMG or NCS were also performed. Sural nerve biopsies were also performed in 2 of 17 (12%) patients with peripheral neuropathy. Patients with liver involvement presented with

Table 1
Clinical Characteristic

Clinical characteristic	Group	n (%)
Age, yr	<56	25 (27)
	≥56	28 (53)
Sex	Male	32 (60)
	Female	21 (40)
Light-chain subtype	Kappa	19 (36)
	Lambda	32 (60)
	Unknown	2 (4)
dFLC (mg/dL) before transplantation	<18	21 (40)
	≥18	21 (40)
	Unknown	11 (20)
Bone marrow	<10%	21 (40)
	≥10%	32 (60)
Bone marrow amyloid	Absence	36 (68)
	Presence	17 (32)
β2 microglobulin (μg/mL)	<3.5	36 (68)
	≥3.5	16 (30)
	Unknown	1 (2)
Serum creatinine (mg/dL)	<2	47 (89)
	≥2	6 (11)
Urine protein 24 h (g/d)	≤1	35 (66)
	>1	17 (32)
	Unknown	1 (2)
Albumin serum	<3.5	15 (28)
	≥3.5	38 (72)
Alkaline phosphatase	≤126	40 (75.5)
	>126	13 (24.5)
Induction type	Novel*	33 (62)
	Conventional	13 (25)
	No induction	7 (13)
Melphalan dose (mg/m^2)	<200	7 (13)
	200	46 (87)
Number of involved organ (including heart and kidney)	1	23 (43)
	2	12 (23)
	3	15 (28)
	4	3 (6)

* Novel therapy defined as IMid or PI-based therapy alone or in combinations.