Melphalan/Total Body Irradiation–Conditioned Myeloablative Allogeneic Hematopoietic Cell Transplantation for Patients With Primary Plasma Cell Leukemia

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Clinical Practice Points

- Primary plasma cell leukemia (pPCL) is an aggressive plasma cell (PC) malignancy. Compared to patients with multiple myeloma, those with pPCL experience shorter durations of progression-free and overall survival (OS) after consolidative autologous stem cell transplantation.
- Myeloablative allogeneic hematopoietic cell transplantation (alloHCT) appears to be an effective anti-PC therapy for patients with pPCL, although high rates of treatment-related mortality have been reported previously.
- Seven patients with pPCL underwent alloHCT conditioning with a dose-reduced myeloablative regimen of melphalan 100 mg/m^2 and 9 Gy of total body irradiation (MEL100/TBI9) at our institution. With a median follow-up of 28.6 months in the 5 patients surviving the immediate posttransplantation period, 4 patients remain alive without evidence of relapsed disease on active observation and 1 patient is alive with relapsed disease and is receiving salvage therapy. Two patients with poorly controlled disease before alloHCT died of sepsis within 2 weeks of stem cell reinfusion.
- Patients with pPCL demonstrating a minimal disease burden after induction therapy may achieve prolonged disease-free survival after myeloablative alloHCT conditioning with MEL100/TBI9.

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Introduction

Primary plasma cell leukemia (pPCL) is an aggressive plasma cell (PC) malignancy that does not respond well to front-line cytotoxic chemotherapy.[1] However, more effective disease control has been achieved with the use of novel agent–containing regimens,[2] and an overall response rate of nearly 80% has been reported in patients with pPCL receiving bortezomib-based therapies.[3]

Similar to patients with multiple myeloma (MM), those with pPCL are frequently offered consolidation with high-dose melphalan followed by autologous stem cell transplantation (ASCT). However, 272 patients with pPCL undergoing ASCT captured within the European Group for Blood and Marrow Transplantation registry achieved a median progression-free survival (PFS) of 14.3 months and a median overall survival (OS) of 25.7 months, which was significantly shorter than that of a large cohort of patients with MM (27.4 months and 62.3 months, respectively).[4] Smaller retrospective series show similar or less favorable survival outcomes for patients with pPCL undergoing ASCT.[2,5]

Allogeneic hematopoietic cell transplantation (alloHCT) has also been incorporated into the management of patients with pPCL. An analysis of 50 patients undergoing alloHCT reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) demonstrated a 3-year PFS rate of 20% and a 3-year OS rate of 38%, along with a 3-year nonrelapse mortality rate of 41%. No statistically significant differences in these outcomes were seen in patients receiving conditioning with myeloablative and reduced-intensity regimens.[5] Larger retrospective studies of patients with MM have also indicated that treatment-related mortality is significantly higher for those undergoing myeloablative alloHCT compared with those undergoing reduced-intensity alloHCT[6,7] and

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ASCT.[8,9] However, data also show that the rate of PFS at 2 years is significantly higher in patients with MM undergoing myeloablative alloHCT compared with those receiving reduced-intensity alloHCT,[6] and the median PFS is significantly longer in patients with MM undergoing myeloablative alloHCT compared with ASCT if they survive > 1 year after transplantation.[8] Despite significant toxicity, long-term OS rates of approximately 40% have been demonstrated in patients with MM undergoing myeloablative alloHCT.[9,10]

It appears that patients with PC malignancies can achieve long-term survival after alloHCT, although the success of this strategy is very much dependent on reducing the incidence of significant toxicity as well as disease relapse given the less potent graft-versus-tumor effect demonstrated in MM as compared to other hematologic malignancies.[11,12] Accordingly, we sought to design a myeloablative conditioning regimen before alloHCT with potent anti-PC activity that would be well tolerated by patients with pPCL. Noting the curative potential of the combination of melphalan (MEL) and total body irradiation (TBI) but the high rate of treatment-related mortality associated with previously reported dosing,[9,13] we treated patients with pPCL using a lower dose myeloablative[14,15] regimen of MEL 100 mg/m^2 and 9 Gy of TBI in 6 fractions (MEL100/TBI9) at our institution and report the outcomes here.

Retrospective Chart Review

Seven patients with pPCL underwent MEL100/TBI9 alloHCT at the University of Pennsylvania between June 2009 and January 2013. MEL was given as a single infusion of 100 mg/m^2 on day −3 and TBI was administered as 150 cGy twice daily on days −2, −1, and 0. Palifermin was given on days −4 (60 mg/kg) and 0 (180 mg/kg) for prevention of mucositis. Methotrexate 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11 along with tacrolimus titrated to a trough of 5 to 15 μg/L were used for graft-versus-host-disease (GVHD) prophylaxis. Tacrolimus was typically tapered starting around day 100 after alloHCT per institutional policy. Therapies before and after alloHCT were given at the discretion of the treating physician. Response was defined using the International Myeloma Working Group response criteria for PCL.[16] Previously reported criteria were used to define acute[17] and chronic[18] GVHD. PFS was defined as the time from alloHCT to disease progression or death. OS was defined as the time from alloHCT to death. Data were collected through August 1, 2013. This study was approved by the University of Pennsylvania Institutional Review Board, with a waiver of informed consent for the retrospective review of patient records.

Results

Baseline characteristics and therapies received before alloHCT are summarized in Table 1. The median age at diagnosis was 48 years (range, 41-57 years). Baseline β2-microglobulin levels were elevated in all patients. Metaphase karyotyping and PC fluorescence in situ hybridization were not routinely performed. The median number of regimens received before alloHCT was 2 (range, 1-4), and most patients received at least 1 therapy containing thalidomide, lenalidomide, or bortezomib.

AlloHCT details and outcomes after alloHCT are summarized in Table 2. The median time from diagnosis to alloHCT was 6.8 months (range, 3.4-9.7 months). Karnofsky performance status score was 70 in 3 patients and 90 in 4 patients. All patients received hematopoietic cells from 10/10 HLA-matched donors, and the source was peripheral blood in almost all cases. Disease responses were stable or improved in patients surviving > 100 days after alloHCT. Unfractionated peripheral blood donor chimerism around 100 days after alloHCT was ≥ 97% in all surviving patients. Two patients received lenalidomide maintenance starting > 100 days after alloHCT. Treatment-related mortality was experienced by 2 patients—1 with progressive disease and 1 with a partial response before alloHCT, with deaths resulting from sepsis occurring at day +7 and +13 after stem cell reinfusion. Excluding these 2 patients, the median length of follow-up was 28.6 months after alloHCT (range, 6.7-49.9 months). For these 5 surviving patients, the median event-free survival and median OS were not yet reached. All patients achieving very good partial response or better before alloHCT remain alive without progressive disease.

Acute GVHD occurred in 2 patients. This affected the intestine in both patients (grade III and unknown grade, respectively) and resolved after treatment with systemic corticosteroids and tacrolimus

Table 1 Baseline Characteristics and Therapy Before AlloHCT

Patient number	1	2	3	4	5	6	7
Age (years)	48	41	44	52	48	57	54
Sex	F	M	F	F	F	F	F
β2-microglobulin (mg/L)	2.6	2.5	4.5	5.7	9.4	5.5	6.7
Conventional cytogenetic analysis	46,XX	Unknown	Unknown	Unknown	46,XX	Complex	45,X,-X, t(6;8),t(11;14)
FISH	Unknown	Unknown	Unknown	Unknown	Unknown	t(4;14)	14q32.3 rearrangement
Immunoglobulin	Lambda LC	Kappa LC	IgG lambda	IgG lambda	Kappa LC	IgA kappa	Lambda LC
Initial induction	CVAD	BorD	CVAD	CVD	BorD	LenBorD	BorDAC
Salvage induction	—	CVAD, DPACE, CAD	CyBorD, DPACE	CVAD	LenD, DPACE	—	BorDT-PACE
Refractory to novel agents	—	Yes	Yes	—	Yes	No	Yes

Abbreviations: alloHCT = allogeneic hematopoietic cell transplantation; BorD = bortezomib, dexamethasone; BorDAC = bortezomib, dexamethasone, doxorubicin, cyclophosphamide; BorDT-PACE = bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; CAD = cyclophosphamide, doxorubicin, dexamethasone; CVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone; CVD = cyclophosphamide, vincristine, dexamethasone; CyBorD = cyclophosphamide, bortezomib, dexamethasone; DPACE = dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide; FISH = fluorescence in situ hybridization; LC = light chain; LenBorD = lenalidomide, bortezomib, dexamethasone; LenD = lenalidomide, dexamethasone.