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Feasibility of Lenalidomide Therapy for Persistent Chronic Lymphocytic Leukemia after Allogeneic Transplantation

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Abstract

In patients with chronic lymphocytic leukemia (CLL), persistence of disease after allogeneic stem cell transplantation (alloSCT) can result in poor outcomes. In an effort to improve these outcomes, patients with persistent CLL who were 90–100 days post alloSCT with no evidence of graft-versus-host-disease (GVHD) were randomized to receive lenalidomide or standard care (withdrawal of immunosuppression followed by donor lymphocyte infusion). Lenalidomide was initiated at 5 mg every other day and increased to 10 mg daily if tolerated in each patient. Of 38 patients enrolled, 17 (45%) met the eligibility criteria for randomization. Of these 17 patients, 8 were randomized to undergo lenalidomide therapy. Five (62%) patients had to stop taking the drug owing to toxicity. The main reason for drug discontinuation was acute GVHD in 43% of patients. This incidence was 11 % in the patients who were randomized to not receive lenalidomide. With a median follow-up of 2.6 years, the median survival was 3.4 years for those receiving lenalidomide. This was not reached in patients randomized to not receive lenalidomide and in patients in

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complete remission who were not randomized. These results suggested that treatments other than lenalidomide are needed for persistent CLL after alloSCT.

Keywords

Lenalidomide; CLL; nonmyeloablative; Allogeneic; Transplantation

INTRODUCTION

Nonmyeloablative allogeneic stem cell transplantation (alloSCT) can induce long-term remissions in 30–40% of patients with heavily pretreated relapsed chronic lymphocytic leukemia (CLL) in whom conventional treatment has failed [1–7]. A major hurdle for CLL patients who undergo alloSCT is a relapse rate of 40–50%.

In a prior study, we found that about half of the transplant recipients with CLL at our center had to undergo immunomodulation (IMM) consisting of withdrawal of immunosuppressive therapy followed by donor lymphocyte infusion (DLI) due to persistent disease 3–6 months after alloSCT [3]. In that trial, the median overall survival (OS) for patients who achieved complete remission (CR) following IMM has not yet been reached with a median follow-up time of 47 months (range, 5.4–110.2 months), whereas the median OS for the patients who did not achieve CR after IMM was 35 months. A more recent 6-months landmark analysis using an international standardized flow-cytometry for detection of minimal residual disease (MRD) suggested an increase in disease-related death in CLL patients who remain MRD+ at 6 months after alloSCT [8]. Chronic graft-versus-host-disease (GVHD), however, remains a significant cause of morbidity after IMM [3, 9] and alternative strategies are needed.

Lenalidomide is an immunomodulator that benefits patients with CLL [10–12] by enhancing antitumor immunity [13–15], but data on its tolerance and activity in CLL patients after alloSCT are scarce. Therefore, we performed this randomized phase 2 trial to incorporate lenalidomide into our post-alloSCT strategy for persistent CLL and compare clinical responses to IMM. This is the first reported randomized trial of lenalidomide in such patients (ClinicalTrials.gov number NCT00899431).

METHODS

Study Design and Eligibility

This investigator-initiated was conducted at The University of Texas MD Anderson Cancer Center (Houston, TX) from May 2009 to November 2012. Initially, the established fludarabine, cyclophosphamide, and rituximab conditioning regimen [3] was used. In August 2011, the conditioning regimen was changed to bendamustine, fludarabine, and rituximab [5] conditioning as new information about this regimen was obtained from another study of lymphoid malignancies [5]. GVHD prophylaxis consisted of tacrolimus, 0.015 to 0.03 mg/kg starting on day −2, and methotrexate, 5 mg/m^2 on days 1, 3, and 6 in all patients. Patients who received a transplant from matched unrelated donors (MUD) received an additional dose of methotrexate at 5 mg/m^2 on day 11. Rabbit antithymocyte globulin (1

mg/kg IV on days −2 and −1 before alloSCT) was given to all patients receiving a MUD transplant.

Patients were randomized at a 1:1 ratio to receive lenalidomide 90–100 days after alloSCT if they had persistent active CLL by computed tomography scans and/or morphological involvement of bone marrow biopsies, had been engrafted with >20% donor T cells, had a creatinine clearance ≥30 mL/min (based on Cockcroft-Gault calculation), did not have acute GVHD and had an absolute neutrophil count of ≥1,500/μL and a platelet count of ≥70,000/μL at the time of randomization. These patients were stratified according to the presence or absence of the 17p deletion, a known adverse prognostic factor associated with resistance to conventional chemotherapy.

Patients who were randomized to receive lenalidomide were maintained on tacrolimus, up to 6 months as per our standard of care, unless they progressed earlier. They underwent IMM, only in case of disease progression while receiving lenalidomide. Patients who were randomized not to receive lenalidomide for persistent disease 90–100 days post alloSCT, underwent immediate IMM. Tacrolimus was withdrawn over one month. Rituximab was given at a dose of 375mg/m^2 intravenously, followed by 3 weekly doses of 1000 mg/m^2. A DLI of 1×10^6 CD3-positive T cells/kg was administered after the first 2 doses of rituximab if no GVHD occurred. An escalated DLI dose was given at 6-week intervals if there was persistent active disease and no GVHD.

Responses to alloSCT in CLL patients were scored according to the recommendations of the National Cancer Institute-Sponsored Working Group [15]. Disease extent was assessed in all patients using computed tomography scans of the chest, abdomen, and pelvis as well as positron emission tomography.

The starting dose of lenalidomide was 5 mg given by mouth every other day. The dose was increased, if tolerated, to 5 mg daily after 28–35 days and then 10 mg daily after an additional 28–35 days.

Statistical Design

The primary objective of this study was to compare the need for IMM in the treatment groups. For this trial, IMM was defined as cessation of immunosuppressive treatment, earlier than our standard of care of 6 months after alloSCT, owing to persistent disease or donor lymphocyte infusión. In a randomized trial of 60 patients, assuming that the need for IMM is reduced from the historical rate in cohorts of CLL patients considered for alloSCT from 49% to 25% with the addition of lenalidomide, the probability that the lenalidomide-arm will be correctly selected as superior is greater than 80%. The trial was monitored by the Data and Safety Monitoring Board (DSMB) at our center.

RESULTS

A total of 38 patients were enrolled on the study (Table 1). Of the 38, 17 (45%) were randomized to the two treatment arms (9 to the non-lenalidomide arm and 8 to the lenalidomide arm); 21 patients (55%) were not randomized to the treatment arms because

they did not meet the randomization criteria. Reasons for non-randomization are listed in Figure 1A.

The maximum tolerated dose of lenalidomide was 5 mg every other day in 3 patients, and 10 mg by mouth daily in four patients. Of the 8 patients who were randomized to receive lenalidomide, one refused to take the drug, and four (57%) of the remaining seven patients had the drug discontinued because of acute liver toxicity and neuropathy (n=1, 14%) or acute GVHD (n=3; 43%). These toxicities occurred at 4, 22, 30, and 37 days after starting the drug (Table 2).

The median duration of lenalidomide administration was 61 days (range, 0–338 days); of those, one patient achieved a CR and two had a partial response as their best response. All 3 of these initial responders subsequently experienced CLL relapse (Table 2). IMM was performed in 57% and 56% of the patients in the groups randomized to receive and not receive lenalidomide, respectively. Three (33% of the 9 patients who were randomized not to receive lenalidomide remain alive and in CR at 24+, 24+ and 48+ months, respectively (Table 3).

All 38 patients enrolled in the study had a median follow-up time of 2.6 years (range, 1.1–5.4 years) after alloSCT. The estimated 3-year OS and progression-free survival rates for the whole group were 51% (95% confidence interval [CI] = 0.36–0.73) and 38% (95% CI = 0.38–0.62), respectively. The median OS was 3.4 years for those receiving lenalidomide. This was not reached in patients randomized to not receive lenalidomide and in the 8 patients who were not randomized as they were in CR 90–100 days post alloSCT (Figure 1B). The median progression-free survival (PFS) was 1.9 years for patients randomized to receive lenalidomide. This was not reached in patients randomized to not receive lenalidomide and in the 8 CR patients.

The cumulative incidence rates of acute grade 2–4 GVHD were 43% (95% CI = 12–0.88) for the patients randomized to receive lenalidomide and 11% (95% CI = 0–0.33) for the patients randomized to not receive lenalidomide.

The mean T cell counts pre- and post-lenalidomide increased for CD3+ (Figure 2A), CD3+/CD8+ (Figure 2B), and CD3+/CD4+ (Figure 2C) by 228/μL, 80/μL, and 147/μL, respectively. In contrast, a rapid decrease in T cells counts was observed for those patients (n = 7) who were randomized not to receive lenalidomide. The mean CD3+, CD3+/CD8+, and CD3+/CD4+ cell counts decreased by 446/μL, 378μL, and 66/μL, respectively, at 6 months post alloSCT. NK cell counts (Figure 2D) were similar in both groups at the same time point.

This trial was closed early upon DSMB’s recommendations at our center, as a result of slow accrual, poor tolerance of lenalidomide, and lack of benefit in the patients who received it.

DISCUSSION

This study is the first randomized trial focused on the applicability of lenalidomide-based treatment in CLL patients who have active disease 90–100 days after alloSCT. The timing of

randomization is based on prior reports of IMM [3] and a 6-months landmark analysis [8] involving MRD status. Lenalidomide was associated with significant toxicity, mainly GVHD, prompting early discontinuation of the treatment. The higher incidence of GVHD may be related to the increase in the mean T cells observed in patients who were randomized to receive the drug. In contrast, we saw a decrease in T cells in patients who were not randomized to receive lenalidomide at the same time points after alloSCT. The findings related to T cells numbers after lenalidomide could be confounded by several factors. This includes direct effect of the drug, acute GVHD, chronic GVHD (one evolving from acute GVHD and 2 were de novo), infections [Cytomegalovirus reactivation (n=1), grade 3 bacteremia (n=1), pneumonia (grade 5, n=1; grade 3, n=1), grade 3 cellulitis (n=2), acute sinusitis (n=1)], and DLI post-chemotherapy (n=1).

The literature has a paucity of data with regard to tolerance and activity of lenalidomide in CLL patients after alloSCT. Researchers have used lenalidomide as post-alloSCT maintenance therapy in multiple myeloma patients with similar results [17,18]. Our present randomized trial differs from those by Kneppers [17] and Wolschke [18] and their colleagues in the GVHD prophylaxis used (cyclosporine A combined with mycophenolate mofetil in the trial by Kneppers et al [17] instead of tacrolimus and methotrexate in our study; the prophylaxis varied in the trial by Wolschke et al [18]). Also differing were the taper schedules for immunosuppression after alloSCT (taper started by day 84 in the trial by Kneppers and colleagues, day 120 in the trial by Wolschke and colleagues, and 6 months after alloSCT in our trial). The intensities of the alloSCT conditioning regimens used differed as well (several patients in the trial by Wolschke and colleagues received myeloablative regimens). Despite these differences, the results of the 3 studies were similar in that acute GVHD was the main reason for discontinuation of lenalidomide use after alloSCT.

Results of this prospective trial were similar to previous historical data [3]. We found similar survival rates in patients who were in CR 90–100 days post alloSCT when compared to the group of patients who received IMM for persistent CLL that was documented by computed tomography scans and/or morphological involvement of bone marrow biopsies. Although these survival rates were not statistically different from those observed in patients who did not receive IMM but instead received lenalidomide, these findings are confounded by the small number of patients and the treatments this latter group of patients received post discontinuation of lenalidomide due to toxicity or progression. This includes ofatumumab, ibrutinib, combination chemo-immunotherapy (oxaliplatin, fludarabine, cytarabine, rituximab) followed by DLI, and checkpoint inhibitor.

Our results suggest that therapy for persistent CLL with lenalidomide 90–100 days after alloSCT is not feasible in this patient subset and that alternative strategies are needed to treat persistent CLL.

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Brief report

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A.

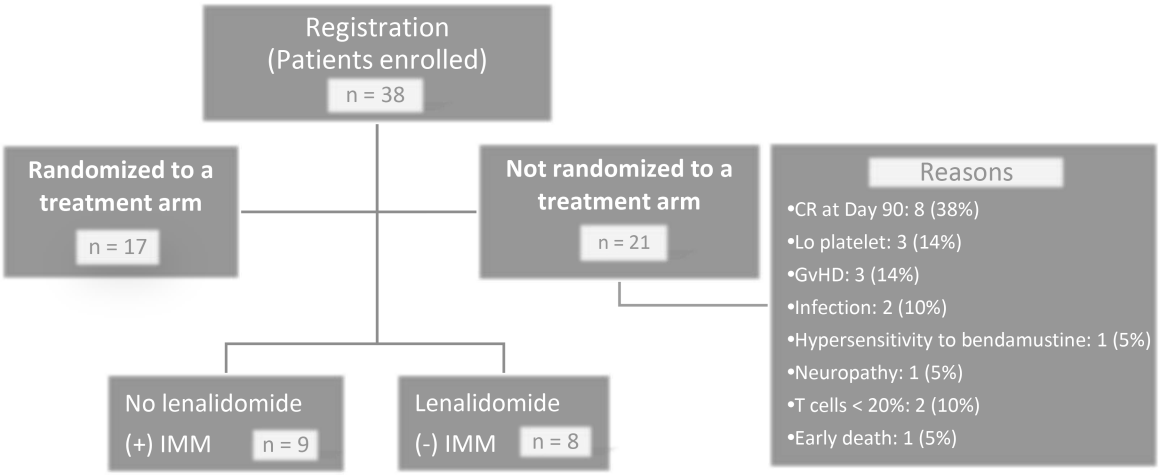

Figure 1A.

Flow diagram of the 38 patients enrolled in our randomized trial of lenalidomide-based treatment of CLL after alloSCT. CR, complete response; Low, platelet count of < 70,000/μL.

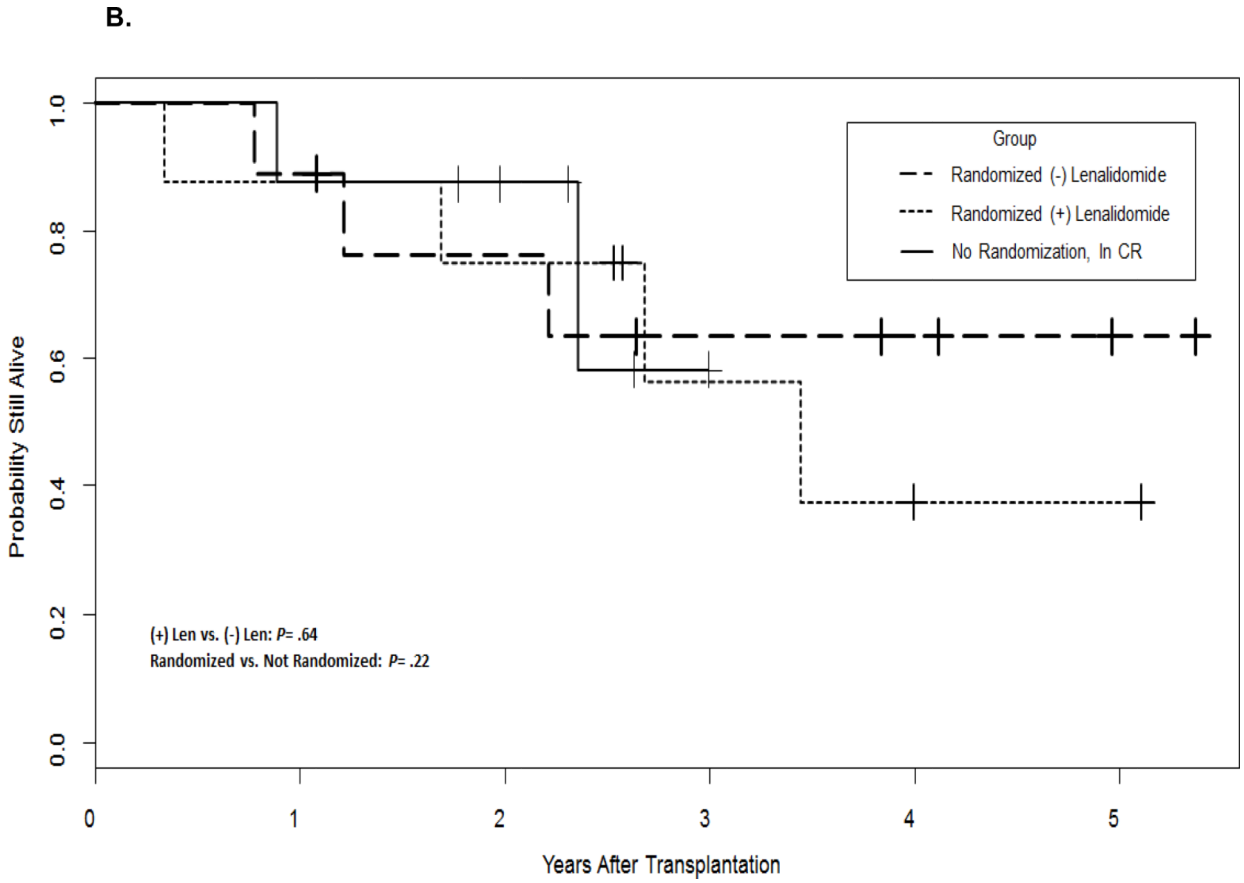

Figure 1B.

OS rates in the CLL patients in our trial after nonmyeloablative alloSCT according to randomization status and whether they received lenalidomide (Len) after transplantation.

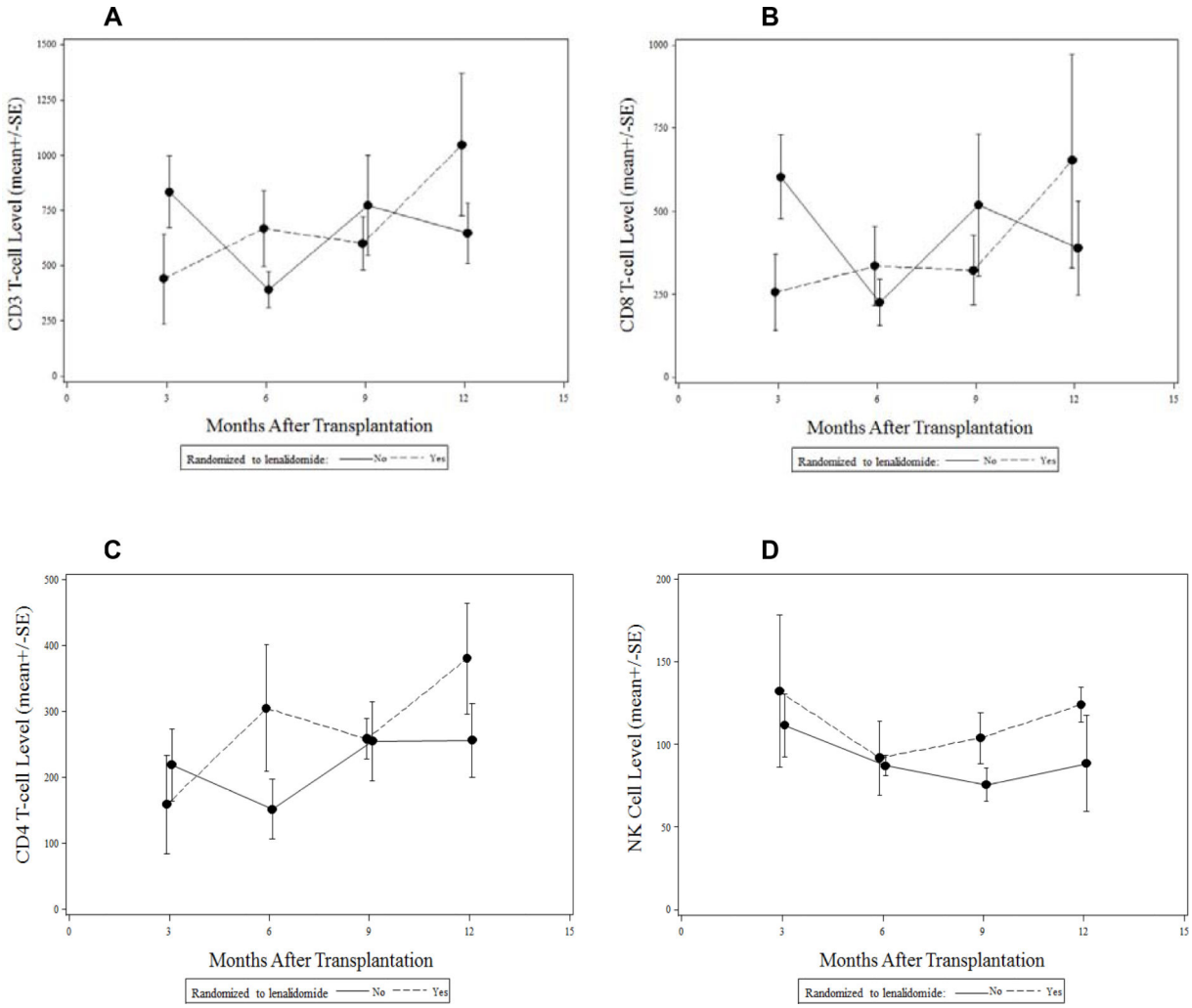

Figure 2. Immune Recovery

A. CD3 T cell recoveries. When compared to pre-starting lenalidomide, the mean CD3+ cell counts increased by 228/μL for those patients (n = 6) randomized to receive the drug at 6 months post alloSCT, corresponding to 3 months after starting lenalidomide. In contrast CD3+ counts decreased by 446/μL in those patients (n = 7) who were randomized not to receive lenalidomide.

B. CD3+/CD8+ T cell recoveries. When compared to pre-starting lenalidomide, the mean CD3+/CD8+ cell counts increased by 80/μL for those patients (n = 6) randomized to receive the drug at 6 months post alloSCT, corresponding to 3 months after starting lenalidomide. In contrast CD3+/CD8+ counts decreased by 378/μL in those patients (n = 7) who were randomized not to receive lenalidomide.

C. CD3+/CD4+ T cell. When compared to pre-starting lenalidomide, the mean CD3+/CD4+ cell counts increased by 147/μL for those patients (n = 6) randomized to receive the drug at 6 months post alloSCT, corresponding to 3 months after starting lenalidomide. In contrast, CD3+/CD4+ celi counts decreased by 66/μL in those patients (n = 7) who were randomized not to receive lenalidomide.

D. Natural Killer (NK) cell recoveries were similar in CLL patients (n = 6) randomized to receive lenalidomide compared with those of the patients (n = 7) randomized to not receive it at 6 months post alloSCT.

Table 1.

Characteristics of CLL patients according to treatment group

Patient/disease characteristic	Total	Not randomized (group 1)	Randomized to lenalidomide		*P* (group 2 *vs*.3)	*P* (group 1 *vs*. 2 + 3)
			Yes (group 2)	No (group 3)		
No. patients	38	21	8	9		
Median age, years (range)	58 (45–72)	60 (49–72)	55 (47–70)	56 (45–72)	.96	.17
Male sex, no. (%)	29 (76)	16 (76)	6 (75)	7 (78)	1.00	1.00
Disease status, no. (%)					.64	.48
Sensitive	26 (68)	16 (76)	4 (50)	6 (67)		
Refractory	12 (32)	5 (24)	4 (50)	3 (33)		
β−2 M > 3 mg/L, no. (%)	12/37(32)	7/20 (35)	3 (38)	2 (22)	.62	1.00
IGHV unmutated, no. (%)	20/21(95)	12/12 (100)	2/3 (67)	6/6 (100)	.33	.43
17p deletion present, no. (%)	11/37 (30)	7/20 (35)	2 (25)	2 (22)	.22	.44
−17p & complex karyotype	3/37 (8)	½0 (5)	2 (25)	0 (0)		
Complex karyotype only	1 (3)	0 (0)	0 (0)	1 (11)		
Median prior lines of therapy, (range)	3 (1–6)	3 (1–6)	2 (1–5)	2 (1–4)	.55	.28
PET +, no. (%)	19/36 (53)	9/19 (47)	5 (63)	5 (56)	1.00	.53
Conditioning type, no. (%)					1.00	.30
BFR	13 (34)	9 (43)	2 (25)	2 (22)		
FCR	25 (66)	12 (57)	6 (75)	7 (78)		
Donor type, no. (%)					1.0	.52
- Matched related	16 (42)	8 (38)	4 (50)	4 (44)		
- Matched unrelated	22 (58)	13 (62)	4 (50)	5 (56)		
Median donor age, (range)	41 (19–70)	37 (19–70)	40 (25–56)	42 (19–63)	.74	.44
ABO mismatch, no. (%)	17 (45)	11 (52)	4 (50)	2 (22)	.33	.51
Sex mismatch, no. (%)	18 (47)	10 (48)	2 (25)	6 (67)	.15	1.00

BFR indicates bendamustine, fludarabine, and rituximab; β−2 M, β−2 microglobulin; FCR, fludarabine, cyclophosphamide, and rituximab; IGhV, IG heavy chain region gene; PET, positron emission tomography.

Table 2.

Outcomes in CLL patients randomized to receive lenalidomide

Patient no.	Dose of lenalidomide	Duration of lenalidomide administration	Reason for lenalidomide discontinuation	Response to lenalidomide	Current status
1	5 mg every other day	45 days	GVHD gr. 2, neutropenia gr. 4	PR	Dead/PD 30 mos
2	5 mg every other day	4 days	Hepatic toxic effects gr. 3, paresthesia gr.2	NE	Alive/ CR 36+ mos
3	5 mg every other day	45 days	GVHD gr. 2	SD	Alive/CR 48+ mos
4	10 mg daily	77 days	Patient's choice	SD	Dead/PD 39 mos
5	10 mg daily	60 days	GVHD gr. 2	SD	Dead Sepsis 2 mos
6	10 mg daily	177 days	Rash	CR (9 mos)	Dead/PD 49 mos
7	10 mg daily	338 days	Patient's choice	PR	Alive/PD 48+ mos
8	Refused	0 days	NA	NA	Dead/PD 20 mos

Gr indicates grade; CR, compete response; gr, grade; NE, not evaluable; PR, partial response; PD, progressive disease; SD, stable disease; mos, months; NA, not applicable.

Table 3.

Outcomes in CLL patients randomized to the non-lenalidomide group

Patient no.	Current status	Cause of death	Post randomization duration (months)
9	Alive/CR	NA	48+
10	Dead	PD	27
11	Alive/PD	NA	35+
12	Alive/CR	NA	34+
13	Dead/CR	GVHD	9
14	Alive/CR	NA	24+
15	Dead	PD	14
16	Alive/PR	NA	24+
17	Alive/PR	NA	13+

CR indicates complete response; NA, not applicable; PD, progressive disease; PR, partial response.