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Lenalidomide Induced Graft Versus Leukemia in a CII Patient Who Relapsed After Allogeneic Stem Cell Transplantion

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Abstract

A 67-year-old male received an HLA matched unrelated peripheral blood stem cell transplant after a non-myeloablative conditioning regimen for heavily pretreated refractory chronic lymphocytic leukemia (CLL) in partial remission. His disease relapsed on day +90 post-transplant with persistent 100% engraftment of the donor cells. Immunusuppression was tapered off by day +96 and he was started on lenalidomide 10 mg per day on day +126. After 6 doses he acutely developed severe hepatitis potentially attributed to the lenalidomide mediated graft-versus-host disease. His liver enzymes slowly improved after cessation of lenalidomide and he achieved complete remission (CR) of the CLL without further treatment, presumably attributed to the graft-versus-leukemia effect induced by lenalidomide. He is alive and in CR over four years after the transplant with no additional therapy.

Introduction

A 67-year-old Caucasian male with heavily pretreated refractory chronic lymphocytic leukemia (CLL) in partial remission was referred to MD Anderson Cancer Center for an allogeneic stem cell transplant (SCT) evaluation.

His history dated back nineteen years to 1993 after which he had several relapses of CLL requiring multiple lines of treatment, as elaborated in Table 1. In June 2009, a positron emission tomography (PET)-CT scan [Figure 1a] showed a partial response and a bone marrow biopsy revealed persistent disease with 30% involvement. Therefore underwent an unrelated peripheral blood SCT (6/3/2009) with a non-myeloablative conditioning regimen: rituximab plus 90Y-ibritumomab, followed by fludarabine (30mg/m2) and cyclophosphamide (750mg/m2) on days -6, -5, -4, and anti-thymocyte globulin (ATG)

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Conflicts of Interest: NONE

0.5mg/kg (day-4), 1mg/kg (day -3), 1.5mg/kg (day -2). Graft-versus-host disease (GVHD) prophylaxis included tacrolimus (starting day -3) and methotrexate 9mg (days 1, 3, 6, 11). His post-transplant course was complicated by cytomegalovirus antigenemia treated with valganciclovir, fungal pneumonia treated with voriconazole, and BK virus cystitis.

On day+84 (8/26/09), the patient was found to have diffuse palpable lymphadenopathy. A PET-CT scan [Figure 1b] and a bone marrow biopsy performed on day+90 (9/1/2009) showed relapsed disease. A biopsy of the inguinal lymph node confirmed the presence of CLL/SLL without transformation. He did not have any evidence of GVHD or infections. His immunosuppression was tapered off by day +96 (9/7/09) and he was started on lenalidomide 10 mg per day with the plan to administer a donor lymphocyte infusion within 4-8 weeks. He received six daily doses of lenalidomide starting day +126 (10/7/09 – 10/12/09) after which he acutely developed severe fatigue, malaise and nausea. His liver enzymes were noted to be markedly elevated, including an alanine aminotransferase of 1322 IU/L (7-56), aspartate aminotransferase of 1239 IU/L (15-46), lactate dehydrogenase of 2573 IU/L (313-618), with normal alkaline phosphatase of 106 IU/L (38-126) and total bilirubin 0.2 mg/dL (0.0-1.0). A comprehensive infectious disease work up and an MRI scan of the abdomen did not reveal any obvious pathology. Lenalidomide was discontinued, after which his liver enzyme abnormalities completely recovered as shown in Table 2. Although unusual without hyperbilirubinemia, the hepatic dysfunction was presumed to be in part GVHD possibly triggered by lenalidomide. No liver biopsy was performed as the liver function tests began improving as soon as lenalidomide was discontinued.

A bone marrow biopsy performed one month later (11/2009) did not reveal any evidence of CLL either morphologically or by flow cytometry. Subsequent CT chest, abdomen and pelvis showed improvement in abdominal lymph nodes and bilateral axillary nodes and the PET scan became FDG negative [Figure 1c]. Two months later, the patient presented with mild violaceous skin rash, consistent with presumed grade I GVHD, which resolved with topical steroids. Subsequent bone marrow biopsies have been negative for CLL; the CT scans showed complete regression of lymphadenopathy and the PET scans have remained FDG negative [Figure 1d]. He has been monitored every 3-6 months and continues to remain in complete remission for over four years without additional therapy. The patient's peripheral blood chimerism assay has persistently shown 100% donor engraftment in the total and T cell fraction.

Discussion

The natural history of CLL is heterogeneous. It can follow an indolent course that can be managed with the “watch-and-wait approach.” It can also behave very aggressively, resistant to most therapies and potentially fatal.[1,2] CLL refractory to purine analogues, such as Fludarabine, is particularly aggressive and carries a poor prognosis with a median survival of 9-10 months.[3,4] Allogeneic SCT can be curative even in certain high-risk patients. With SCT, the 5-year overall survival ranges from about 50% to 83%; the better responses have been noted particularly with the reduced-intensity conditioning regimens in recent years. [5-7]

Lenalidomide belongs to the “immunomodulatory” class of drugs. It is active against a variety of hematological disorders including, multiple myeloma [8-10], amyloidosis[11], myelodysplastic syndrome[12,13], myelofibrosis with myeloid metaplasia,[14] non-Hodgkin's lymphoma,[15] and CLL – both upfront and in relapsed setting. [16] Its precise mechanism of action is still unclear and is disease specific. It favorably affects several key immunological pathways related to tumorigenesis and progression, such as alterations in cytokine production and activations of NK-and T-cells. For example, a phase II study[17] using lenalidomide in treatment-naïve CLL patients showed that their baseline proportions of IL-2, INF-γ and TNF-α secreting CD4+ cells and activated CD8+ cells were elevated as compared to healthy individuals. These proportions decreased significantly and became comparable to those in healthy individuals after 15 cycles of treatment. The percentage of regulatory T-cells (Tregs), which is known to be inappropriately increased in patients with CLL,[18] also decreased significantly after 15 cycles. Another study[19] using lenalidomide in 44 heavily pretreated relapsed/refractory CLL patients noted significant increases in plasma levels of cytokines such as IL-2, IL-6, IL-10 and TNF- α by day 7 of the treatment. Collectively, these findings suggest that the clinical activity of lenalidomide in CLL is complex and may involve cell-mediated cytotoxicity.

Because of this potential effect on cell-mediated cytotoxicity and modulation of cytokines, lenalidomide may also elicit GVHD as well as graft-versus leukemia (GVL) effects after allogeneic SCT. In fact, lenalidomide-induced acute GVHD resulted in early termination of a prospective phase-II trial assessing its role in patients with acute myeloid leukemia and myelodysplastic syndrome after allogeneic SCT, despite apparent GVL effects by lenalidomide.[20] Similar high rates of acute GVHD observed in another study led Kneppers et al [21] to conclude that lenalidomide maintenance for multiple myeloma after allogeneic SCT was not feasible. It is conceivable that the GVHD and GVL effects are likely related to the immunomodulatory effects. For example, in a phase I/II study[22] of lenalidomide maintenance in multiple myeloma patients post-transplant, several changes were noted in the surface expression of various activating receptors on NK cells without an absolute increase in their number. Specifically, the NKp30 and NKp44 expression increased significantly, without any changes in the inhibitory receptors such as the NKG2A or KIR-receptors after treatment with lenalidomide compared to the baseline values. The *in-vitro* NK cell lytic activity against the myeloma cell line improved significantly after 1 and 2 months of treatment compared to the pre-treatment levels. Similarly, several changes were noted in the T-cell profile. The levels of INF-γ secreting CD8+ T-cells increased significantly after 2 weeks and CD4+ T-cells after 3 months of the treatment, although both of these had started to rise within a week. Tregs, which decreased transiently, demonstrated significant increase after 3 months. These activations in NK- and T-cells were significantly less in patients who did not respond to lenalidomide. Another study [21] demonstrated activated profiles of T- and NK cells, with significant increase in HLA-DR expression on CD4+ and CD8+ T-cells by day 15 of starting lenalidomide maintenance after allogeneic SCT for multiple myeloma.[21]

Although the classical acute liver GVHD generally follows a cholestatic pattern with hyperbilirubinemia and high alkaline phosphatase level, the hepatic-variant GVHD is also being increasingly recognized, which presents with significant elevation of transaminases.[23,24] The key pathological change in classical-GVHD is the portal tract

lymphocytic infiltration with preserved hepatocellular structure. Hepatic-variant GVHD on the other hand manifests as lobular necrosis, acidophil bodies and minimal bile duct changes mimicking acute viral hepatitis.[23-28] Clinically, the hepatic-variant GVHD lasts longer compared to the classical type (74 vs. 32 days, P =0.006); however, with no significant differences in the use of immunotherapy for GVHD, resolution of acute GVHD, occurrence of chronic GVHD, and GVHD-related mortality.[24]

As the GVHD and the GVL effects often go hand-in-hand,[29] lenalidomide-induced GVHD may potentially translate to improved outcomes; however, this remains to be explored. The role of lenalidomide in CLL patients post-allogeneic SCT is being assessed in a randomized clinical trial, the details of which can be found at *ClinicalTrials.gov*, NCT00899431.

Conclusion

Our patient with refractory aggressive CLL, which had relapsed after multiple treatments, relapsed within 90 days of the allogeneic SCT. After discontinuing the immunosuppression, he was started on lenalidomide 10 mg daily as a bridge to potential donor lymphocyte infusion. He received only six doses of the drug that precipitated severe hepatic injury, the etiology of which was attributed to possible hepatic-variant GVHD triggered by lenalidomide. Without further intervention, the patient attained complete remission, which has endured for over 4 years from the transplant. The occurrence of GVHD after lenalidomide therapy has been reported in multiple myeloma patients after an allogeneic SCT, but not in CLL. Thus the role of lenalidomide in CLL in the post-transplant setting requires further investigation.

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Clinical Practice Points

What is already known about this subject?

The clinical course of chronic lymphocytic leukemia (CLL) is highly variable - ranging from an indolent course to an aggressive fatal disease. Fludarabine resistant CLL in particular carries a poor prognosis. Allogeneic stem cell transplantation (SCT) is the only curative option for patients with aggressive disease, but the outcomes are not absolute.

What are the new findings?

Lenalidomide may potentially induce graft-versus-host disease (GVHD) as well as a graft-versus-leukemia (GVL) effect in patients with relapsed CLL post-transplant.

How might it impact on clinical practice in the foreseeable future?

Lenalidomide may have a role in the treatment of relapsed CLL post-transplant; however the balance between the GVHD and the GVL effects needs to be monitored closely.

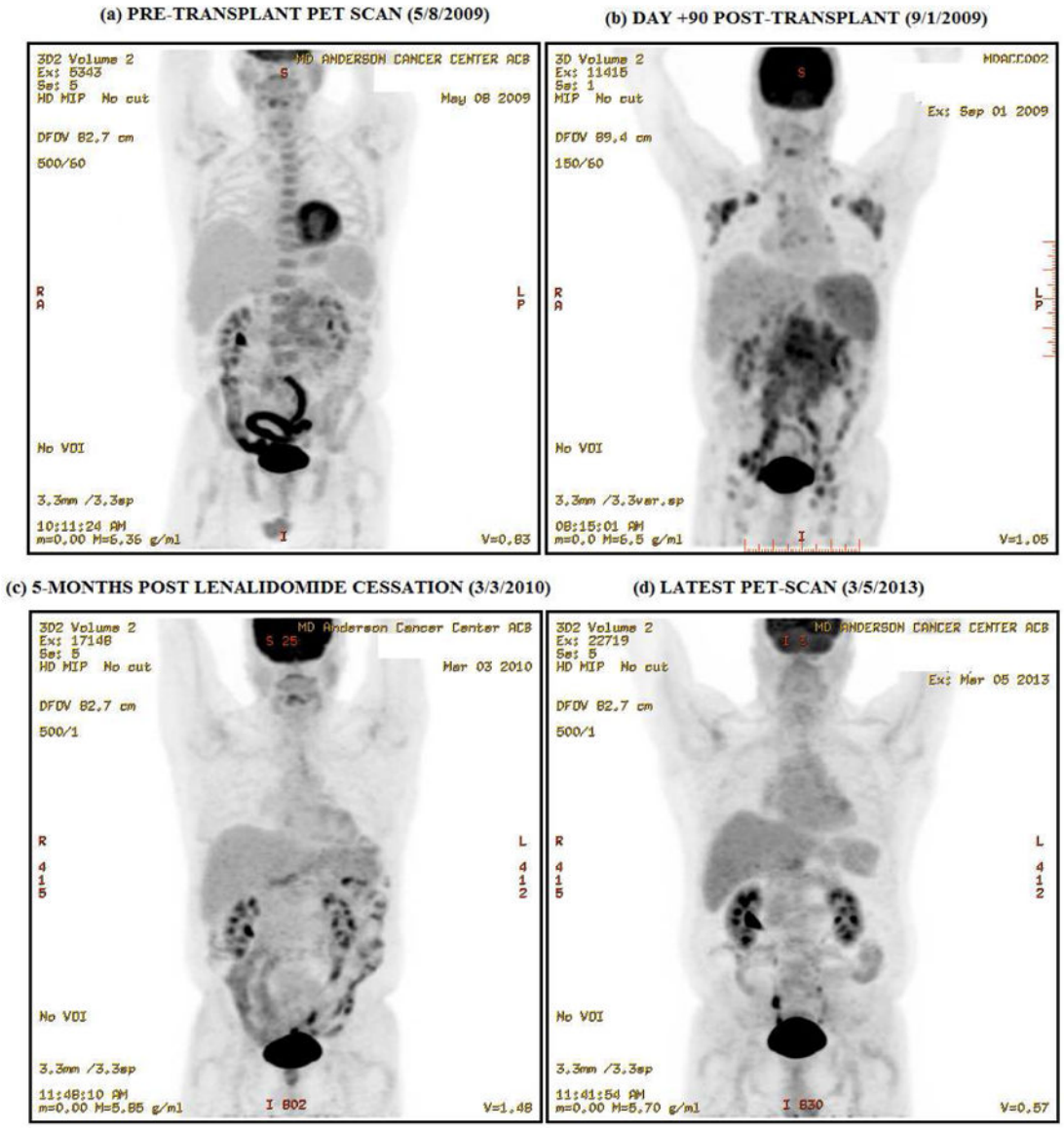

Figure 1. Pet Scans

Table 1

Outline of Clinical Course

Date	Day post-transplant	Clinical Course	Management	Outcome
11/1993		Periaortic lymphadenopathy seen on MRI spine	Observed	
05/1994		Multiple lung nodules on Chest x-ray Progression of adenopathy on CT scan of abdomen. A FNA of a right lung nodule showed Cryptococcus Neoformans		Treated with Fluconazole
02/1995		Biopsy of a retroperitoneal lymph node showed SLL/CLL	Observed	
02/1995		BM biopsy showed CLL/SLL	Observed	
1999		Progressive adenopathy	Cyclophosphamide + Prednisone	Complicated by the Cryptococcal N. pneumonia treated with amphotericin. CLL in CR
02/2001		BM biopsy: 60-70% involvement with CLL. Cytogenetics: trisomy 12; confirmed by FISH.	Bcl-2 antisense clinical trial	Complicated by toxic cholestatic hepatitis. Progression of CLL
04/2001			FCR X 6	CR
09/2005		BM biopsy: no evidence of CLL		
02/2006		BM biopsy: 20-30% CLL; 95% ZAP-70 positive.	FCR X 6	MRD
2/14/2008		Nodal progression	Weekly Rituximab + Methylprednisolone	Progression
9/2008			FCR X 3	Progression
1/26/2009			OFAR	Poor platelet recovery + Progression
3/2009			Hyper-CVAD plus Rituximab X 3	Partial response. Course complicated by *C. diff*, treated with Vancomycin
6/3/2009	**Day 0**		**Allo SCT**	
9/1/2009	**Day +90**	PET-CT and BM biopsy showed relapsed CLL.		
9/7/2009	**Day +96**	**Tacolimus discontinued**		
9/8/2009	**Day +97**	FNA lymph node positive for SLL/CLL without transformation		
10/7/09 – 10/12/09	**Day +126-Day +131**		**Lenalidomide 10mg daily X 6 doses**	**Acute severe hepatitis**
11/17/2009	**Day +167**	BM biopsy: negative for CLL		CR
1/3/2010	**Day +214**	PET-CT scan – dramatic improvement in lymphadenopathy without F-18 FDG avidity		CR
6/8/2010	**Day +370**	BM biopsy: negative for CLL		CR

Date	Day post-transplant	Clinical Course	Management	Outcome
1/4/2011	**Day +580**	BM biopsy: negative for CLL PET-CT scan: no evidence of F-18 FDG avid malignancy		CR
7/11/2011	**Day +568**	PET-CT scan: no evidence of F-18 FDG avid malignancy		CR
3/2/2012	**Day +1003**	BM biopsy: negative for CLL		CR
3/5/2013	**Day +1371**	BM biopsy: negative for CLL PET-CT scan: no evidence of F-18 FDG avid malignancy		CR

FCR: Fludarabine, Cyclophosphamide, Rituximab; OFAR: Oxaliplatin, Fludarabine, Cytarabine, and Rituximab; Allo SCT: allogeneic hematopoietic stem cell transplant; CR: complete response' MRD: minimal residual disease; BM: bone marrow; FNA: fine needle aspiration; SLL/CLL: small lymphocytic lymphoma/chronic lymphocytic leukemia; PET: positron emission tomography; CT: computed tomography; FDG: Fluorodeoxyglucose; *C. diff*: Clostridium difficile

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Table 2

Laboratory Data

Date	Day post-transplant	AST	ALT	Alk Phos	T bili	LDH
		IU/L (15-46)	IU/L (7-56)	IU/L (38-126)	MG/DL (0.0-1.0)	IU/L (313-618)
6/3/2009	Day 0		21	73	0.3	938
7/6/2009	Day +33		14	70	0.2	637
9/1/2009	Day +90		14	108	<0.2	2902
9/25/2009	Day +114		19	71	0.2	1382
10/7/09 – 10/12/09	Day +126-Day +131	Lenalidomide 10mg daily X 6 doses				
10/13/2009	Day +132	**1239**	**1322**	**106**	0.5	**2573**
10/15/2009	Day +134	**1207**	**1514**	**144**	0.3	**1793**
10/17/2009	Day +136	**394**	**977**	**193**		**868**
3/3/2010	Day +273	35	24	93	0.5	417

AST: aspartate aminotransferase; ALT: Alanine transaminase; Alk Phos: Alkaline Phosphatase; T.bili: Total bilirubin; LDH: lactate dehydrogenase; IU/L: International Units/liter