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Consolidation treatment with lenalidomide following front-line or salvage chemoimmunotherapy in chronic lymphocytic leukemia

The anti-tumoral activity of lenalidomide occurs via multiple mechanisms, including repair of chronic lymphocytic leukemia-induced immune defects.¹ We therefore hypothesized that it would be an effective and safe consolidation strategy in patients with chronic lymphocytic leukemia (CLL) who have residual disease after treatment.

In this phase II trial, we recruited patients with CLL who had achieved either partial remission (PR) (including nodular PR [nPR]) or complete remission (CR) with evidence of bone marrow minimal residual disease (MRD)

on flow cytometry after either front-line or salvage chemoimmunotherapy. Consolidation therapy with lenalidomide was started after a minimum of 3 months to a maximum of 9 months from the completion of chemoimmunotherapy. The trial conformed to the Declaration of Helsinki and was approved by the MD Anderson institutional review board.

Oral lenalidomide was given at a dose of 10 mg daily for 3 months and could be reduced to 2.5 mg daily in the presence of toxicity; after the first 12 patients were enrolled, the protocol was amended to allow up to 12 months of treatment for the subsequent 20 patients. Response improvement (RI), the primary endpoint, was assessed at 4 and 12 months, and residual disease was measured in the bone marrow by 4-color flow cytometry with a sensitivity of at least 0.02%. The treatment was to

Table 1. Patient characteristics at start of consolidation therapy (n=32).

Characteristic	Median [range], number (percentage)		
	All patients (n=32)	After front-line therapy (n=13)	After salvage therapy (n=19)
Age (years)	59 [38-79]	57 [38-76]	63 [41-79]
Males	19 (59)	6 (46)	13 (68)
White blood count (10 ⁹ /μL)	4.4 [1.9-16.2]	4.4 [2.7-6.1]	4.6 [1.9-16.2]
Absolute neutrophil count (10 ⁹ /μL)	2.7 [0.7-7.5]	2.7 [1.2-4.1]	3 [0.7-7.5]
Absolute lymphocyte count (10 ⁹ /μL)	0.8 [0.2-5.7]	0.9 [0.3-2]	0.8 [0.2-5.7]
Hemoglobin level (g/dL)	13.3 [10.8-14.7]	13.2 [11.6-14.3]	13.4 [10.8-14.7]
Platelet count (10 ⁹ /μL)	154 [79-275]	151 [90-275]	154 [79-242]
eGFR level (mL/min)	82 [44-128]	81 [68-128]	83 [44-105]
Immunoglobulin G (mg/dL)	541 [105-1570]	616 [243-1210]	468 [105-1570]
CD3 (cells/uL)	554 [7-1076]	569 [115-923]	545 [7-1076]
CD4 (cells/uL)	202 [2-572]	218 [55-534]	193 [2-572]
CD8 (cells/uL)	206 [5-865]	180 [51-561]	207 [5-865]
Beta-2-microglobulin level (mg/L)	2.5 [1.5-4.3]	2.4 [1.5-4.3]	2.5 [1.6-4.2]
FISH			
13q deletion	7/28 (25)	3/12 (25)	4/15 (27)
Negative	14/28 (50)	5/12 (42)	8/15 (53)
Trisomy 12	2/28 (7)	1/12 (8)	1/15 (7)
11q deletion	5/28 (18)	3/12 (25)	2/15 (13)
<i>IGHV</i> unmutated	13/20 (65)	4/8 (50)	9/12 (75)
> 2 previous lines of therapy	19 (59)	0 (0)	19 (100)
Most recent therapy			
FCR	22 (69)	10 (76)	12 (62)
CFAR	2 (6)	1 (8)	1 (9)
BR	2 (6)	0 (0)	2 (10)
OFAR	2 (6)	1 (8)	1 (9)
R-hyper-CVAD	2 (6)	0 (0)	2 (10)
R-CHOP	1 (3)	1 (8)	0 (0)
R+GMCSF	1 (3)	0 (0)	0 (0)
Baseline disease status			
CR with MRD positivity	8 (25)	4 (31)	4 (21)
PR/nPR	24 (75)	9 (69)	15 (79)

eGFR: estimated glomerular filtration rate; FISH: fluorescence *in situ* hybridization; *IGHV*: immunoglobulin heavy variable gene; FCR: fludarabine, cyclophosphamide, and rituximab; CFAR: alemtuzumab, fludarabine, cytarabine, and rituximab; BR: bendamustine and rituximab; OFAR: oxaliplatin, fludarabine, cytarabine, and rituximab; R-hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R+GMCSF: rituximab and granulocyte macrophage colony-stimulating factor; CR: complete remission; MRD: minimal residual disease; PR: partial remission; nPR: nodular partial remission.

Table 2. Grade 3-4 adverse events.

Adverse event	After front-line therapy (n=13)	After salvage therapy (n=19)	All patients (n=32)
Neutropenia, no. (%)	5 (38)	11 (58)	16 (50)
Infection, no. (%)	1 (8)	4 (21)	5 (16)
Thrombocytopenia, no. (%)	0 (0)	2 (10)	2 (6)
Pulmonary embolism, no. (%)	0 (0)	1 (5)	1 (3)

be considered promising if RI was 45% or higher. Progression-free survival (PFS) was calculated from the date of initiation of consolidation therapy with lenalidomide to the date of progression requiring treatment or death, and patients were censored at the time of last follow up. Toxicity was assessed using the Common Toxicity Criteria version 3.0. Thirty-two patients were enrolled in the study from March 2008 through September 2012 (data cut-off was September 2016). At the time of initiation of lenalidomide consolidation, 8 patients (25%) were in CR with positive MRD, and 24 patients (75%) were in PR (including 8 patients in nPR). Thirteen patients (41%) received consolidation after front-line therapy, and 19 patients (59%) received consolidation after 2 or more lines of treatment (Table 1). Lenalidomide consolidation was started after a median of 7 months (range, 3-9 months) following completion of chemoimmunotherapy. Treatment duration for each patient is shown in Figure 1. The median daily dose of lenalidomide was 10 mg (range, 5-10 mg). Five (16%) patients discontinued treatment because of toxicity; 3 of them (9%) had treatment interrupted after 2, 7, and 20 days of therapy and were considered evaluable for toxicity, but not for response or PFS.

RI was observed in 13 patients (45%) (Figure 1). Four of the 8 patients who entered consolidation therapy with nPR improved to CR (2 negative for MRD). Seven of the 15 patients with PR improved to CR (1 negative for MRD), and 2 of the 15 patients with PR improved to nPR. Six (55%) RIs were observed among the 11 patients who received lenalidomide after front-line therapy, and 7 (39%) RIs were observed among the 18 patients who received lenalidomide after salvage therapy.

After a median follow up of 47 months (range, 7-94 months), 20 patients (69%) progressed; the median PFS for the entire group was 30 months (95% confidence interval, 20-40 months). Median PFS for the 13 patients with RI was 39 months (range, 7-92). The median PFS for the 11 patients that received lenalidomide after initial therapy was 43 months, compared to 29 months for the 18 patients that received lenalidomide after salvage therapies. The association of patient characteristics and PFS was evaluated, and a trend for shorter median PFS was observed for patients receiving consolidation with lenalidomide after salvage therapy compared with patients who received consolidation with lenalidomide after front-line therapy (29 vs. 43 months; $P=0.08$).

Treatment-related toxicity effects in all 32 patients are shown in Table 2. Among the 16 patients who had grade 3-4 neutropenia, infectious complications were observed in only 5 patients. Neutropenia in these patients resolved with dose reduction or transient discontinuation of lenalidomide, and growth factor support was not given in this study. No grade 5 adverse events were observed.

One patient experienced an episode of pulmonary

embolism after only 2 doses of lenalidomide; this patient had received 5 previous lines of treatment and developed this complication while hospitalized for pneumonia.

Reasons for early discontinuation (within the first month) of lenalidomide therapy were pulmonary embolism (grade 3) with concomitant pneumonia in 1 patient, skin rash (grade 2) in 1 patient, and persistent fatigue (grade 2) in 1 patient.

Our experience showed that consolidation therapy with lenalidomide can be well tolerated in the majority of cases and can improve response to chemoimmunotherapy in patients with CLL.

Two trials of lenalidomide as consolidation have been reported: Shanafelt *et al.* reported on 34 patients who received lenalidomide consolidation shortly after front-line pentostatin, cyclophosphamide, and rituximab; the median daily dose was 2.5 mg and median duration was 6 cycles; RI was seen in 24% of patients, and median PFS was not reached, after a median follow up of 37 months.² Correlative studies conducted in these patients suggested that the benefit of lenalidomide consolidation strategies depends on the ability of lenalidomide to repair T-cell synapse activity and enhance long-term T-cell function. The shorter time to the start of lenalidomide and the lower median daily dose of lenalidomide in that study when compared with our experience may explain, at least in part, the lower rate of RI (24% vs. 45%).

Chang *et al.* reported the results of lenalidomide consolidation in 19 patients with CLL who had residual or stable disease after salvage treatment with bendamustine and rituximab (BR). Lenalidomide was administered at a dose of 5-10 mg for up to 12 cycles, starting 6-12 weeks after the completion of BR therapy. RI was reported in only 1 patient (5%), and the median PFS was 18 months.³ The lower rate of RI (5% vs. 39%) and the shorter PFS (18 months vs. 29 months) observed in this study, compared with those outcomes in the 19 patients in our study who were also treated after salvage therapy, could be due to the study's higher rate of lenalidomide discontinuation (13 of 19 patients) and the inclusion of patients with stable disease after treatment with BR.

In our previous experience of lenalidomide as an initial therapy for CLL, the median time to best response was 25 months,⁴ significantly longer than the treatment duration employed in the above-mentioned studies.^{2,3} Unfortunately, data about median time to response were not yet available at the time of our study design; as a consequence, a limited-duration consolidation was chosen for this study.

The early results of 2 randomized studies of lenalidomide as maintenance therapy have been recently reported as conference abstracts.^{5,6} The German CLL Study Group conducted a phase III, double-blinded randomized study, evaluating the efficacy of lenalidomide maintenance compared with placebo among patients who had

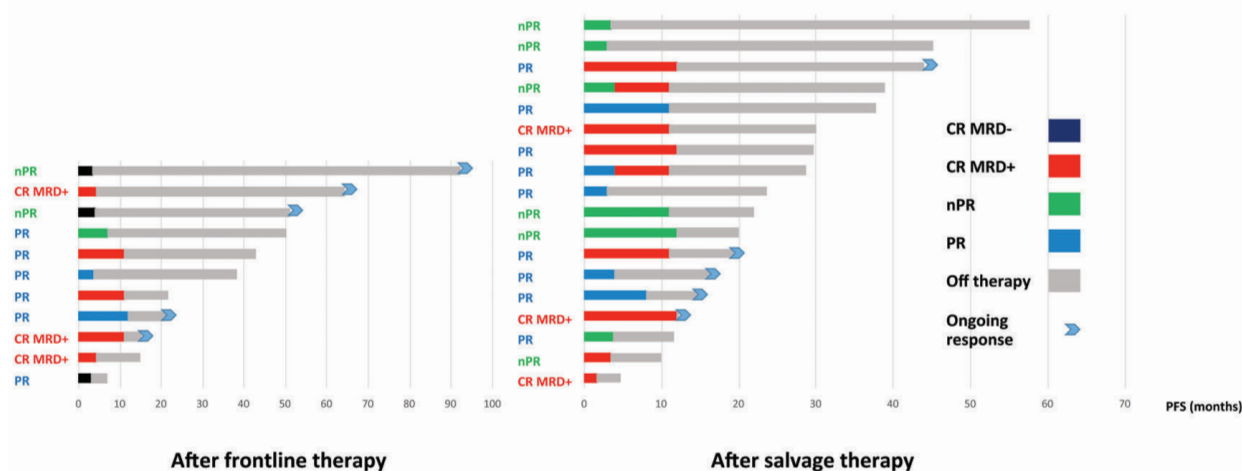


Figure 1. Response improvement and progression free survival. (A) After front-line therapy. (B) After salvage therapy. CR: complete remission; MRD: minimal residual disease; PR: partial remission; nPR: nodular partial remission. Three patients who discontinued treatment before first response assessment were not evaluable for response and/or survival.

residual disease after front-line fludarabine, cyclophosphamide, and rituximab, and carried at least one unfavorable prognostic factor. Lenalidomide was started at a dose of 5 mg daily, escalated up to 15 mg, and continued until progression or intolerable toxicity. Eighty-nine patients were randomized to receive lenalidomide (60 patients) or placebo (29 patients). The median PFS in the patients randomized to lenalidomide was not reached after a median follow up of 18 months and was significantly longer compared with the median PFS of 15 months in the 29 patients randomized to the placebo arm ($P < 0.001$), with a relative risk reduction for progression of $>80\%$ for the patients receiving maintenance therapy with lenalidomide. Compared with placebo, lenalidomide was more frequently associated with neutropenia (30% vs. 3% of patients); however, no difference was observed in terms of infections (50% vs. 62%).

The second study of maintenance therapy with lenalidomide, reported by Foa *et al.*, was a phase III randomized study of lenalidomide maintenance compared with placebo following second-line treatment. The treatment plan consisted of a starting dose of lenalidomide of 2.5 mg/day and subsequent escalation to 10 mg/day. A total of 314 patients were enrolled, and assignment to the lenalidomide (160 patients) and placebo (154 patients) arms was based on their response at the end of second-line treatment and the presence of adverse prognostic factors. The median PFS was 58 months for the patients treated with lenalidomide and 33 months for the patients assigned to the placebo arm ($P < 0.001$). The most common adverse events in this study were neutropenia and diarrhea, and they were more common with lenalidomide than with placebo (neutropenia, 66% vs. 30%; diarrhea, 41% vs. 16%). The rate of severe infections was similar in patients treated with lenalidomide or placebo (17% vs. 10%), despite a difference in the incidence of neutropenia.

In conclusion, lenalidomide is an effective consolidation strategy for CLL patients treated with chemoimmunotherapy, with RI observed in 45% of patients and a median PFS from the time of lenalidomide initiation of 30

months. With the current rapid evolution of therapeutic approaches in CLL, our experience provides a rationale for investigating lenalidomide as a consolidation strategy given concomitantly with or sequentially to therapy with newer targeted therapies.

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References

- Jain N, O'Brien S. Targeted therapies for CLL: Practical issues with the changing treatment paradigm. *Blood Rev.* 2016;30(3):233-244.
- Shanafelt TD, Ramsay AG, Zent CS, et al. Long-term repair of T-cell synapse activity in a phase II trial of chemoimmunotherapy followed by lenalidomide consolidation in previously untreated chronic lymphocytic leukemia (CLL). *Blood.* 2013;121(20):4137-4141.
- Chang JE, Havighurst T, Kim K, et al. Bendamustine + rituximab chemoimmunotherapy and maintenance lenalidomide in relapsed, refractory chronic lymphocytic leukaemia and small lymphocytic lymphoma: A Wisconsin Oncology Network Study. *Br J Haematol.* 2016;173(2):283-291.
- Strati P, Keating MJ, Wierda WG, et al. Lenalidomide induces long-lasting responses in elderly patients with chronic lymphocytic leukemia. *Blood.* 2013;122(5):734-737.
- Foa R, Schuh A, Zaritskey A, et al. Results of the Phase 3 Study of lenalidomide versus placebo as maintenance therapy following second-line treatment for patients with chronic lymphocytic leukemia (the CONTINUUM Trial). *Blood.* 2016;128(22):230.
- Fink AM, Bahlo J, Sandra R, et al. Lenalidomide maintenance after front line therapy substantially prolongs progression free survival in high risk CLL: interim results of a phase 3 study (CLL M1 study of the German CLL Study Group). *Blood.* 2016;128(22):229.