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A Phase II Randomized Study of Lenalidomide or Lenalidomide and Rituximab as Maintenance Therapy Following Standard Chemotherapy for Patients with High/High-intermediate risk Diffuse Large B-Cell Lymphoma

Nishitha M. Reddy, MD[1], **John P. Greer, MD**[1], **David S. Morgan, MD**[1], **Heidi Chen, PhD**[2], **Steven I. Park, MD**[3], and **Kristy L. Richards, MD**[4]

[1]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville

[2]Department of Biostatistics, Vanderbilt University Medical Center, Nashville

[3]Division of Hematology/Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill

[4]Division of Hematology/Oncology, Weill Cornell Medical College, New York

Keywords

Lenalidomide; Diffuse Large B-Cell Lymphoma; rituximab

Diffuse large B-cell lymphoma (DLBCL) is curable in about 2/3 of patients with R-CHOP immunochemotherapy. Risk stratification of DLBCL that employs the International Prognostic Index (IPI) is a robust predictive prognostic model, developed more than two decades ago and grouped patients into four categories with a 2-year survival of 34% in the highest risk group(1). The revised IPI confirmed the prognostic ability of these factors in the rituximab era, stratifying the outcome of patients using similar prognostic markers and regrouping patients into 3 categories: patients with 3 or more risk factors had the worst PFS

Corresponding Author: Nishitha M. Reddy MD, MSCI, Associate Professor of Medicine, Division of Hematology/Oncology, Department of Medicine, 3927 The Vanderbilt clinic, 1301 Medical center Drive, Tel: 615-936-0381, Nishitha.reddy@vanderbilt.edu.

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of 53% (2). Despite overall improvements with rituximab, the prognosis continues to remain poor in patients with high risk features.

Lenalidomide is an oral immunomodulator with direct anti-tumor activity and indirect anti-neoplastic actions through its immunologic effects. Our group and others previously showed that len induces antiproliferative effects against lymphoma cell lines (3, 4). Increased number and functional activity of NK cells were demonstrated in pre-clinical models treated with len (5). The anti-tumor effects of len were augmented by rituximab associated antibody-dependent cellular cytotoxicity (6).

We postulated that maintenance therapy may eradicate residual disease and prevent the emergence of chemotherapy resistant disease clone. In this study we evaluated the role of len monotherapy with or without rituximab following R-CHOP in patients with intermediate-high to high risk DLBCL.

Adult patients with newly diagnosed DLBCL in complete remission after standard front line therapy with R-CHOP chemotherapy with or without radiation with high or high-intermediate risk IPI (>3 if age >60 years or >2 if age less than 60 years) were included in the study. Patients were randomized to one of the two arms within 4-12 weeks of completing chemotherapy or radiation.

Patients in arm A received len 25 mg daily, Days 1-21, followed by 7 days of rest (28-day cycle). Cycles were repeated every 28 days for a total of 12 cycles. Patients in arm B received len 20 mg daily, days 1-21, followed by 7 days rest (28-day cycle). Rituximab was administered at a dose of 375 mg/m^2 intravenously on Day 8 of Cycle 1 of len and repeated on Day 8 of odd numbered cycles (Cycles 1, 3, 5, 7, 9, and 11) for a total of 6 doses from randomization. Patients received thromboprophylaxis with aspirin unless they required treatment for known thrombosis. Per protocol, imaging studies were performed every 3 months for the first year of randomization.

The primary endpoint of the study is to assess the one-year relapse-free survival for patients treated with len alone (Arm A) or the combination of len and rituximab (Arm B). The current standard therapy of DLBCL is treatment with immuno-chemotherapy with rituximab and CHOP and 40% of patients in the high or high-intermediate risk groups experience a relapse as early as one year (7). The expectation is that a 25% difference of relapse will have clinical significance when compared to historical controls. A sample size of 64 patients was recommended at initial enrollment that also accounted for a drop out rate of 10%. At interim analysis, response rates were noted to be higher than expected. With a sample size of 22 in each arm, we estimated 80% power to detect a difference of 25% between the null hypothesis that the one year relapse is 40% and the alternative hypothesis that the one year relapse is 15% using a two-sided significance level of 2.5%. Therefore an adjusted total enrollment of 44 patients was planned. Response assessment was based on previous standards that include Cheson criteria for NHL. Data analysis was performed on an intention-to-treat basis. This clinical trial was registered with NCI at clinicaltrials.gov *(NCT00765245)*

Forty-four patients were enrolled between February 2008 and August 2013. Baseline characteristics of patients receiving maintenance therapy are listed in table 1.

At a median follow up of 3.64 years, in the intent-to-treat population, the one-year DFS and OS were 89% and 91% respectively. The two-year DFS and overall survival (OS) were 86% (72%-94%) and 91% (77%-96%), respectively. For patients in arm A and arm B the one-year DFS were 95% and 86%, respectively. The two-year DFS was 86% (63% - 95%) vs. 86% (62% - 95%) and the two-year OS was 86% (62% - 95%) vs. 95% (72% - 99%) , respectively *(P=NS)*. A subset analysis on the outcome of patients based on cell of origin was performed. The PFS and OS were not statistically different between the two groups (Figure 1). Five patients had disease relapse, including 2 patients while receiving study drug. Three of these patients died due to disease progression and 2 patients are alive after receiving salvage therapy that included autologous stem cell transplant. One death occurred during the study period that was secondary to a surgical procedure and unrelated to the study drug.

The most common grade 3-4 toxicities included neutropenia (57%), fatigue (13%), diarrhea (9%), rash (9%). Nausea and vomiting occurred in 2 patients. One patient developed deep vein thrombosis that was related to disease progression. Hyperuricemia occurred in one patient. Related grade 1-2 toxicities include endocrine abnormalities [hypo/hyperthyroidism] in 29.5% and rash 65%. Other grade 1-2 toxicities that were reported in at least 15% of patients included diarrhea, constipation, anemia, hyperglycemia, nail changes and thrombocytopenia. Two pts discontinued treatment due to adverse events, one patient due to fatigue and the other patient withdrew from the study. One patient was diagnosed with colon cancer after completion of maintenance therapy. (supplementary table 1)

Per the protocol, dose modifications were made only in len (supplementary table 2). During treatment, dose reductions to level −1 (20 or 15 mg) were made in 9 patients, dose level −2 (15 or 10 mg) in 12 patients and to level −3 (10 or 5mg) in three patients. Most of the dose reductions occurred during cycle 2-5 of the planned 12-month treatment. Cytokine analysis was performed on patients pre and post treatment with len. (supplementary figure).

Strategies to overcome the negative impact of high-risk IPI include intensifying induction therapy by adding newer agents to standard therapy, consolidating therapy by using sequential agents following induction therapy, or maintenance strategies for a defined period. Treatment intensification with regimens such as rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (R-ACVBP) or an infusional regimen with rituximab, etoposide, prednisone, vincristine, doxorubicin and cyclophosphamide (R-EPOCH) both showed some benefit for low IPI patients, but not for high-risk patients (8). The addition of novel agents such as bortezomib, ibrutinib, and other newer agents to the existing backbone of R-CHOP is an exciting approach, but studies with these agents have not yet shown benefit in the frontline setting.

Consolidative autologous stem cell transplant in patients with high-intermediate or high-risk aggressive B or T-cell NHL following chemotherapy demonstrated improvement in PFS but not in OS.(9) Furthermore, this approach is not feasible in older patients or in patients with

organ compromise. Enzastaurin, a potent inhibitor of PKCβ, also demonstrated no clinical benefit when used in combination with R-CHOP, even with a maintenance phase included (10, 11).

Our data show that immunomodulatory therapy following initial chemo-immunotherapy in a high risk group of patients appears promising and support the use of len following R-CHOP therapy in patients with high-risk diffuse large B-cell population. We did not observe an added benefit of rituximab to lenalidomide. Our study interpretations may be limited by the small number of patients and potentially a highly selected group of patients.

Len, as a single agent has activity in relapsed/refractory DLBCL with an overall response rate of 19-28% (12). Len when combined with R-CHOP appeared to be effective in untreated DLBCL (13) Nowakowski et al., combined len with R-CHOP therapy in newly diagnosed DLBCL, the results of which suggested that the negative prognostic impact of non-GC can be overcome with the addition of len (14). In the current study, we did not identify the preferential action of len in either subgroup, although the small sample size could explain this.

Recent data suggests that patients with DLBCL treated with standard immunochemotherapy who remain event-free 2 years (EFS-24) following the diagnosis have an excellent outcome with an overall survival similar to the general population. These results suggest EFS-24 as a surrogate primary end point while designing future trials as observing patients beyond 24 months added little benefit(15). The 2-yr DFS of 86% in our study is encouraging in this high-risk group of patients and may reflect an overall survival benefit, although it is unknown whether the kinetics of DLBCL relapse are the same after len treatment. Longer follow up will be informative to determine this.

The treatment related side effects that occurred during the year long therapy were expected and manageable. The primary hematological adverse event was myelosuppression that was managed with dose modifications. The incidence of thyroid abnormalities was higher than previously reported and may have indirectly contributed to fatigue.

Our data support the evaluation of an ongoing randomized phase 3 study comparing len to placebo maintenance in this patient population by the LYmphoma Study Association (LYSA) (NCT01122472)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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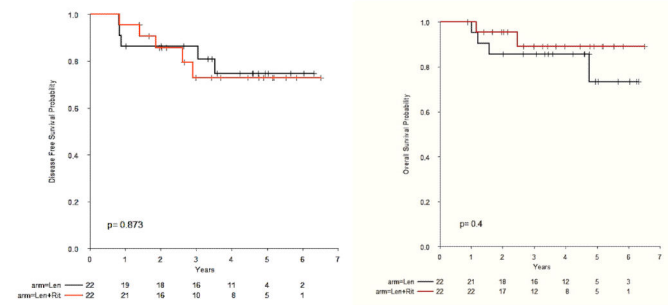

Fig 1a,b

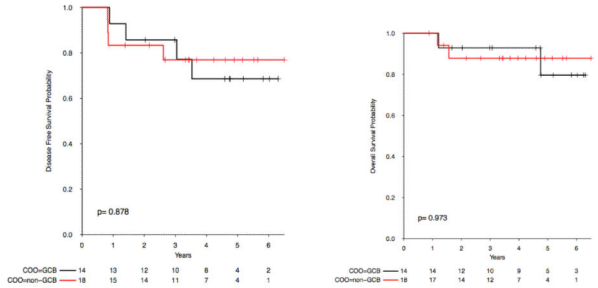

Fig 1c,d

Fig 1.

(a) Disease free survival and (b) Overall survival of patients by treatment arm (c) disease free survival and (d) overall survival by cell of origin

Table 1

Baseline characteristics

Patients	Lenalidomide n (%)	Lenalidomide + rituximab n (%)	Total n (%)
Patients	22 (50%)	22 (50%)	44
Gender Female Male	12 (54.5%) 10	9 (40.9%) 13	21 (47.7%) 23
Age (range in yrs) Median	61 yrs	60 yrs	19-85 60 yrs
IPI score (age adjusted) 3 4 5	4 (18.1) 10 (45.4%) 8 (36.3%)	4 (18.1%) 14 (63.6%) 4 (18.1%)	8 (18.1%) 24 (54.5%) 12 (27.2%)
Stage III **Stage IV**	7 (31.8%) 15 (68.1%)	4 (18.1%) 17 (77.2%)	11 (25%) 32 (72.7%)
Elevated LDH	10 (45.4%)	7 (31.8%)	17 (38.6%)
Prior XRT	1	2	3
Cell of origin *Germinal center type* *Non-Germinal center type* *unknown* *T-cell rich B cell* *EBV positive DLBCL*	16* 18 5 4 1 *two patients had double hit lymphoma (*MYC/BCL2*) by FISH		