Title: A Phase 2 study of Lenalidomide, Rituximab, Cyclophosphamide and Dexamethasone (LR-CD) for Untreated Low Grade Non-Hodgkin Lymphoma Requiring Therapy

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Abstract:

Patients with indolent NHL have multiple treatment options yet there is no consensus as to the best initial therapy. Lenalidomide, an immunomodulatory agent, has single agent activity in relapsed lymphoma. This trial was conducted to assess feasibility, efficacy and safety of adding lenalidomide to rituximab, cyclophosphamide, and dexamethasone (LR-CD) in untreated indolent NHL patients requiring therapy.

This was a single institution phase II trial. Treatment consisted of IV rituximab 375mg/m$^2$ day 1, oral lenalidomide 20mg days 1-21, cyclophosphamide 250mg/m$^2$ days 1, 8, 15, and dexamethasone 40mg days 1, 8, 15, 22, of a 28-day cycle. Treatment continued 2 cycles beyond best response for a maximum of 12 cycles without rituximab maintenance.

Thirty-three patients were treated. Median age was 68 (43-83 years). 39% had stage IV disease. Histologic subtypes included: 8 follicular lymphoma (FL), 7 marginal zone lymphoma (MZL) (1 splenic, 2 extranodal, 4 nodal), 15 Waldenström’s macroglobulinemia (WM), 1 lymphoplasmacytic lymphoma, 1 small lymphocytic lymphoma, and 1 low-grade B-cell lymphoma with plasmacytic differentiation (unable to be classified better as MZL or LPL). Hematologic toxicity was the most common adverse event. Median time of follow up was 23.4 months (range 1.8-50.9). The overall response rate was 87.9%, with 30.3% complete response. The median duration of response was 38.7 months. The median PFS was 39.7 months, while median OS has not yet been reached.

Lenalidomide can be safely added to a simple regimen of rituximab, oral cyclophosphamide, and dexamethasone and is an effective combination as initial therapy for low-grade B cell NHL.

Key words: non-Hodgkin lymphoma, indolent, lenalidomide, low-grade

Clinical trial register: NCT00784927

Introduction:

Indolent lymphomas are often advanced stage at presentation, tend not to be curable, and frequently follow a recurrently relapsing and remitting course. Low grade (indolent) non-Hodgkin lymphomas (NHL) include: follicular lymphoma (FL, grade 1 and 2), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia (LPL/WM), and marginal zone lymphoma (MZL, nodal and extranodal). Chemotherapy, immunochemotherapy, radiation, and radioimmunotherapy are options for those requiring treatment. Novel effective first line
combination therapies with limited toxicity and durable response rates are needed for low grade lymphomas.

Historically, standard treatments in the pre-rituximab era for this patient group included cyclophosphamide, vincristine, and prednisone (CVP) and single agent fludarabine. With the advent of the monoclonal antibody rituximab, response rates generally improved and immunochemotherapy became the new standard. As a single agent, rituximab is a reasonable choice for patients with advanced stage indolent lymphoma and low burden of disease with response rates approaching 70% [1-4]. Adding rituximab to CVP (RCVP) resulted in improved overall response rates (ORR), CR rates, and time to progression (TTP) [4]. Similarly, adding rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)(RCHOP) improved ORR, duration of response (DOR), and OS [3]. Bendamustine plus rituximab (BR) was associated with significantly longer progression free survival (PFS), higher CR rate and better tolerance compared to RCHOP in a phase III non-inferiority trial without OS benefit [5]. Based on these studies, BR, and RCHOP are common initial therapies for indolent B cell NHL patients. Debate continues as to which regimen is best for initial therapy as none to date has shown any OS advantage [5, 6-9]. Recently, the Bruton tyrosine kinase inhibitor ibrutinib has been approved for treatment of WM offering patients a targeted alternative to chemotherapy [10].

Lenalidomide is an oral immunomodulatory analogue of thalidomide with single agent activity in lymphoproliferative and plasmacytic disorders. Its effects in lymphoproliferative disorders are pleiotropic and include: direct cytotoxicity, immunomodulation, blockade of angiogenesis, and stimulation of natural killer and T cells [11]. The antineoplastic effects appear to require the
presence of cereblon, a ubiquitin ligase protein and the proposed molecular target of lenalidomide [12]. The results of multiple studies of lenalidomide in lymphoma have recently been summarized [13].

Rituximab plus lenalidomide (R²) is active in relapsed/refractory aggressive NHL [14]. A phase I/II trial of R² established a maximum tolerated dose (MTD) of 20mg/day days 1-21 and demonstrated activity in relapsed/refractory MCL [15]. In a second study, untreated advanced stage indolent NHL patients (FL, MZL, SLL) received lenalidomide and rituximab without rituximab maintenance. ORR and CR/CRu rates were impressive with some patients also achieving molecular responses [16]. A recent randomized phase II study comparing R² to lenalidomide alone in relapsed refractory FL patients found ORR and CR to be superior in the combination arm without excessive toxicity [17].

While R² shows good activity in patients with indolent NHL, the addition of cytotoxic agents with anti-lymphoma activity to this well tolerated regimen may improve clinical response rates. Lenalidomide has been safely administered alongside cyclophosphamide and dexamethasone in multiple myeloma [18]. Given the activity of all three agents in lymphoma, we chose to combine the them with the addition of rituximab.

There are limited data on the efficacy and safety of lenalidomide combined with immunochemotherapy in treatment naïve indolent NHL patients. Lenalidomide had been combined safely with oral cyclophosphamide and dexamethasone, therefore, a phase I trial was not necessary [18]. This phase II single arm study was designed to assess efficacy, toxicity, PFS, and OS of the combination of lenalidomide, rituximab, cyclophosphamide, and dexamethasone (LR-CD) in patients
with untreated low grade B cell NHL. Following an interim analysis, the WM cohort was expanded for further study.

**Methods-patients:**

**Patient Selection**

Patients ≥ 18 years of age with histologically confirmed indolent NHL: FL (grades 1 or 2), SLL, MZL, or LPL/WM ≤ 6 months prior to registration were eligible. Patients were previously untreated and in need of treatment in the opinion of the investigator. Measurable disease by MRI or CT scan with lymph nodes ≥ 2 cm in at least one dimension was required. LPL/WM patients without lymphadenopathy must have had > 10% lymphocytes, lymphoplasmacytic cells or plasma cells on bone marrow aspirate/biopsy, and quantitative IgM ≥ 400mg/dL. Additional eligibility criteria included: ECOG performance status of ≤ 2, absolute neutrophil count (ANC) ≥ 1400/mm³, platelet count ≥ 100,000/mm³, creatinine ≤ 2mg/dL, bilirubin ≤ 1.5mg/dL, AST and ALT ≤ 2x ULN (or ≤ 5x UNL if liver metastases), and negative pregnancy test for women of childbearing potential. All study participants were registered into the RevAssist© program, and were willing and able to comply with the requirements. Prophylactic aspirin (325 mg) orally daily was required (intolerant patients were allowed warfarin or low molecular weight heparin). Patients were excluded if they were pregnant or nursing, had significant cardiac comorbidities, known HIV, hepatitis infections, active malignancy requiring treatment, prior intolerance to thalidomide, or previous exposure to lenalidomide.

**Patient evaluation**

Baseline evaluation included history and physical examination; laboratory testing: CBC, chemistries, SPEP and quantitative immunoglobulins; bone marrow biopsy; CT chest, abdomen, and pelvis
(PET/CT was acceptable); and EKG. Adverse event assessments were recorded at baseline and prior to each cycle as per NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAEv3.0). CT scans were repeated prior to odd numbered cycles if nodes were measurable at baseline. Repeat CT scans were not required for WM patients, in whom IgM was monitored as criteria for response. A repeat bone marrow biopsy was required to confirm CR in patients if positive at baseline. Patients were actively followed every 3 months after completing therapy until progression or 5 years from registration. During observation, CT scans were repeated every 3 months through year one then every 6 months years 2 through 5.

This trial was registered as NCT00784927. All patients provided written informed consent. The protocol was approved by the institutional review board and carried out according to the guidelines of good clinical practice and with ethical standards for human experimentation.

**Treatment:**

This was a phase II study designed to assess feasibility and response to lenalidomide, rituximab, cyclophosphamide, and dexamethasone (LR-CD) in patients with symptomatic untreated low grade NHL. Treatment consisted of IV rituximab 375mg/m² on day 1, oral lenalidomide 20mg days 1-21, cyclophosphamide 250mg/m² days 1, 8, 15, and dexamethasone 40mg days 1, 8, 15, 22, of a 28 day cycle. All patients received aspirin 325mg daily. Treatment continued 2 cycles beyond best response for a maximum of 12 cycles. No maintenance therapy was planned. Allopurinol 300mg orally daily (cycle 1 d1-14) was strongly recommended for tumor lysis prophylaxis. Prophylactic Bactrim DS (or equivalent) Monday, Wednesday, and Friday weekly continuing for 3 months beyond treatment was required. Blood products and growth factors were allowed as clinically warranted.
Lymph node measurements were taken from CT, CT portion of the PET/CT or MRI.

Lymphadenopathy measurement was determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions. Measurable extranodal disease was assessed similarly. The spleen was considered nodal disease. Disease that was only assessable (i.e. pleural effusions, bone lesions) was recorded as present or absent unless an abnormality noted by physical examination or imaging was found to be histologically negative.

Response was assessed using the 2007 Revised Response Criteria for Malignant Lymphoma [19]. Response measurements were taken after cycles 2, 4, 6, 8 and at treatment discontinuation. All partial and complete responses were confirmed with another efficacy measurement no less than 4 weeks apart. Therapy was discontinued for patients with progressive disease. For WM, CR was defined as resolution of all symptoms, normalization of serum IgM level with complete disappearance of IgM paraprotein by immunofixation, resolution of any adenopathy or splenomegaly, and no new lesions. This study was designed prior to the updated guidelines in 2013 requiring a bone marrow biopsy as part of response assessment for WM.

Statistical analysis

This was a phase II study design used to assess the efficacy of LR-CD in patients with symptomatic untreated low grade NHL and was designed to test the null hypothesis that the CR rate would be no less than 20%. The initial study design included 28 patients with a proposed CR rate of 20-30% warranting further study. Following completion, the sample size was increased to allow for estimation of the CR rate within the WM subgroup. Secondary endpoints included OS (defined as time from registration to death of any cause), PFS (defined
as time from registration to earliest date of documented disease progression), time to
treatment failure (TTF)(defined as time from registration to date of removal from study – due
to progression, AE, or refusal) and DOR. The Kaplan-Meier method was used to estimate PFS,
OS, time to TTF and DOR.

**Results:**

This study opened November 10, 2008 and was closed to accrual March 8, 2013 with 36 patients
enrolled at Mayo Clinic (10 Mayo Clinic Arizona, 26 Mayo Clinic Rochester). One patient withdrew
prior to initiating treatment, one was deemed ineligible, and one was considered a major treatment
violation (calculated 622mg rituximab dose rounded up to 700mg) during cycle 1. Thirty-three
patients were evaluable and included in the statistical analysis.

**Patient Characteristics**

Patient characteristics are summarized in Table 1. Thirteen patients (39.3%) had stage IV disease.
Thirty patients (90.9%) had extra-nodal disease. One patient had bulky (>10cm) nodal disease. For
patients with WM, the median serum IgM was 4480 mg/dL (1740-7890 mg/dL). Four (27%) WM
patients had grade 2 anemia and 2 (13%) had grade 3 anemia at enrollment.

**Response**

The ORR for all 33 patients was 87.9% (29/33), with 30.3% CR (10 patients: WM 1/15, FL 6/8, MZL
3/7) and 57.6% (19/33) partial response (PR). One patient had stable disease (SD), one progressed,
and two were not assessed for response (one patient refusal and one splenectomy). Of the 15
evaluable WM patients, the ORR was 80% with 1 CR and 11 (73.3%) PR. The median DOR for all
patients was 38.7 months (range 26.8-not reached [95% CI 26.9-not reached]). The median PFS of all patients was 39.7 months; the median OS has not yet been reached (Figures 1A, B). For the WM group, median PFS was 38.3 months and median OS has not been reached.

All patients have completed treatment with a median follow-up of 23.4 months (1.8-50.9 months). The majority of patients tolerated treatment, with 75.8% completing treatment per protocol.

Thirteen patients had delays in treatment (mainly due to cytopenias) and 18 patients required dose reductions due to neutropenia. The median number of cycles was six (1-12 cycles). Early discontinuations were due to: patient refusal (3 pts), progression (2 pts), adverse events (2 pts), and alternate therapy (1 pt). At this time, 30 patients remain alive and three have died, all due to lymphoma. Twenty one (64%) patients remain progression free while 12 (36%) have progressed.

Toxicity

All 33 treated patients were assessed for adverse events (AE). AE ≥ grade 3 regardless of attribution are shown in Table 2. While anemia occurred frequently (28/33 patients), 82% of these AE’s were grade 1 or 2. Grade 1/2 thrombocytopenia occurred in 19 patients, with ≥ grade 3 toxicity in 3 patients (10.7%). Neutropenia ≥ grade 3 occurred in 50% of patients with one episode of febrile neutropenia (3%). Five patients (15%) experienced thrombotic events (4 occurred during treatment [3 pulmonary emboli; 1 B/L UE DVT]; 1 PE occurred during observation). Four new primary malignancies were reported during follow-up: skin cancer (2 pts: one melanoma, one non-melanoma), hematologic malignancy (myelodysplasia), and breast cancer.

Discussion:
LR-CD is a rationally designed, tolerable, and effective treatment strategy for untreated indolent NHL with durable responses. This combination offers the advantage of an alkylating agent combined with immunomodulatory agents that have demonstrated independent activity in low grade lymphomas, with the convenience of a predominantly oral regimen. In this study, treatment with LR-CD resulted in an ORR of 87.9%, comparable to well established alternatives (RCHOP/RCVP ORR 91%; BR ORR 97%), with nearly a third achieving CR (BR CR 31%; RCHOP/RCVP CR 25%)[6]. Median DOR, without maintenance rituximab, was 38.7 months.

Other studies have moved lenalidomide upfront for the untreated patient. In one phase II trial, lenalidomide and rituximab were combined (without an alkylating agent) as first line in multiple indolent B cell NHL subtypes. Response rates were high (90%) and CR rates were 87% (FL), 43% (MZL), and 23% (SLL) respectively [16]. A similar study in FL patients with recurrent disease, concluded R² was more active than lenalidomide alone [20], leading to a multicenter study (CALGB 50803) evaluating R² for untreated FL grade I-3A resulting in ORR 93% and CR rate of 72% [21]. These two studies set the stage for a large phase III international study (RELEVANCE) comparing R² with R-chemotherapy in patients with untreated FL.

In our study, ORR (87.9%) was comparable to R² response rates however direct comparisons are difficult as neither of the above referenced R² studies included patients with WM. The overall CR rate with LR-CD was 30.3%. While response was appreciated across all subtypes, lower CR rates were seen with WM (1/15 CR; 73% PR rate) and MZL (43% CR) compared to FL (75% CR). For responders, outcomes were durable with estimated PFS of 39.7 months (38.3 months for WM).

One limitation of this study is the size and relatively small number of patients with FL and MZL.
A unique feature of our study was the large number (n=15) of patients with WM. When evaluating the WM cohort as a subgroup, we found an 80% ORR with the majority achieving a PR because of small residual M-proteins. In a phase II study of 72 untreated WM patients, cyclophosphamide, dexamethasone, and rituximab (DRC) was tolerable and resulted in ORR of 83% [22]. A prior study combining lenalidomide with rituximab in WM raised feasibility concerns as significant anemia occurred [23]. With LR-CD, patients were able to continue, in spite of hematologic toxicity, suggesting this regimen is highly active and safe even in a population frequently challenged by anemia at presentation.

Toxicities with LR-CD were predictable and manageable. While 5 patients experienced ≥ grade 3 anemia, these were primarily WM patients with significant anemia at study enrollment. Aspirin has been shown to be beneficial for thrombosis prevention in patients on lenalidomide and was required in this study [24]. Venous thromboembolism (VTE) occurred in five patients; however, one patient was not on ASA prophylaxis when the VTE was diagnosed. This incidence is comparable with the incidence of VTE in multiple myeloma studies (5-15%), but higher than seen in single agent lenalidomide studies [13, 25] and in lymphoma patients as estimated by meta-analysis (6%) [26].

Larger trials are needed to enable a true comparison of lenalidomide based therapy with traditional immunochemotherapy. Results of the RELEVANCE study will be enlightening as to whether a non-chemotherapy approach is at least as effective as immunochemotherapy in untreated FL. Our results contribute to the growing body of evidence that lenalidomide can be safely combined with other active agents in the treatment of indolent B cell NHL. Larger studies combining lenalidomide with immunochemotherapy and inclusion of biomarkers predictive of response would be of further
interest to help define the optimal use of lenalidomide as its activity across many subtypes will likely improve current treatment of indolent B cell NHL.

**Legend:**

Figure 1A/B: 1A. Progression-free survival (N=33, Events=13, Median=39.7 months, 95% CI= 28.7 – Not Reached). 1B. Overall survival (N=33, Events=3, Median=Not Reached)

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**Acknowledgment:** The authors acknowledge and would like to thank Daniel David Johnson and Kristianna Maier who served as the clinical research associates for this study.

**References:**


Table I. Patient Characteristics

<table>
<thead>
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<th>Characteristic</th>
<th>n=33</th>
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<td>Age</td>
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<tr>
<td>Median</td>
<td>68</td>
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<tr>
<td>Range</td>
<td>43-83</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Female</td>
<td>9 (27%)</td>
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<tr>
<td>Male</td>
<td>24 (73%)</td>
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<td>Ethnicity</td>
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<td>Non-hispanic</td>
<td>33 (100%)</td>
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<td>WHO classification</td>
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<tr>
<td>CLL/SLL</td>
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<tr>
<td>Marginal zone lymphoma</td>
<td>7 (21%)</td>
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<tr>
<td>Splenic</td>
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<td>Nodal</td>
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<tr>
<td>Extramedullary</td>
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<tr>
<td>Follicular lymphoma</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Waldenstrom’s macroglobulinemia</td>
<td>15 (45%)</td>
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<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Stage (Ann Arbor)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>IV</td>
<td>29 (39%)</td>
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<tr>
<td>Median LDH at baseline</td>
<td>163 (71-343)</td>
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<td>Lymph nodes &gt; 10cm (Bulky disease)</td>
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<td>Yes</td>
<td>1 (3%)</td>
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<tr>
<td>No</td>
<td>32 (97%)</td>
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Abbreviations: WHO – World Health Organization
CLL/SLL – chronic lymphocytic leukemia/small lymphocytic lymphoma
Table II. Adverse events (regardless of attribution)
Abbreviations: ANC - absolute neutrophil count

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<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
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<tr>
<td></td>
<td>n (%)</td>
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<tr>
<td>Fatigue</td>
<td>21 (64%)</td>
<td>9 (27%)</td>
<td>3 (9%)</td>
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<td>Anemia</td>
<td>14 (42%)</td>
<td>8 (24%)</td>
<td>4 (12%)</td>
<td>2 (6%)</td>
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<tr>
<td>Neutropenia</td>
<td>1 (3%)</td>
<td>13 (39%)</td>
<td>8 (24%)</td>
<td>6 (18%)</td>
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<tr>
<td>Leukopenia</td>
<td>8 (24%)</td>
<td>10 (30%)</td>
<td>6 (18%)</td>
<td>2 (6%)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>15 (45%)</td>
<td>4 (12%)</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
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<tr>
<td>Rash</td>
<td>7 (21%)</td>
<td>6 (18%)</td>
<td>1 (3%)</td>
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<tr>
<td>Nausea</td>
<td>11 (33%)</td>
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<tr>
<td>Diarrhea</td>
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<td>2 (6%)</td>
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<td>Thrombosis</td>
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<td>1 (3%)</td>
<td>4 (12%)</td>
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<td>Pneumonia (G3/4 ANC)</td>
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<td>Febrile neutropenia</td>
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Figure 1: Survival Curves

1A. Progression-free survival (N= 33, Events = 13, Median=39.7 months, 95% CI= 28.7 – Not Reached).
Figure 1 Survival Curves
1B. Overall survival (N=33, Events=3, Median=Not Reached)