Efficacy and Safety Profile of Lenalidomide vs Lenalidomide + R-CHOP in patients with Diffuse Large B Cell Lymphoma: A Systematic Review

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A R T I C L E  I N F O

Key Words:
DLBCL, Lenalidomide, Lenalidomide + R-CHOP

How to Cite:

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Received Date: 10th July, 2023
Acceptance Date: 21st August, 2023
Published Date: 31st August, 2023

I N T R O D U C T I O N

Non-Hodgkin lymphomas (NHL) are classified into numerous subtypes, with the aggressive diffuse large B-cell lymphoma (DLBCL) being the most frequent [1]. DLBCL is characterized by its diffuse organization, mature B-cell phenotype, and cell shape, as well as its various subtypes and genetic profiles. There are two types of germinat centers, according to the Hans classification: germinal centre type (GCB) and non-germinal centre type (NGCT) (non-GCB, encompasses most of the activated B-cell type, known as ABC-type) [2]. The conventional treatment for DLBCL is immunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). It cures 50-60% of patients, although patients with relapsed/refractory (R/R) DLBCL have a poor result [3]. Despite significant progress in understanding the genetic and molecular profile of DLBCL over the last few years, there has been limited success in transferring this information into effective upfront therapies. Recently the inclusion of various medications to improve outcomes has drawn significant attention.
Lenalidomide, a derivative of thalidomide, is an immunomodulatory agent that shows fewer side effects such as myelosuppression. In preclinical studies, Lenalidomide was found to have antineoplastic properties that boost cytotoxicity mediated by T and NK cells, as well as immunologic properties that inhibit tumour cell growth and angiogenesis in addition to directly killing cancer cells [4-6]. It not only acts through several routes, but it has also been proven to work on a wide range of hematologic malignancies, including but not limited to multiple myelomas and B-cell NHL [7, 8]. Lenalidomide is a well-tolerated medicine that, when paired with R-CHOP against DLBCL, makes it a potential therapy choice for such individuals[9]. According to long-term follow-up combined results from two phase II studies, the combination of Lenalidomide and R-CHOP maintained its efficacy over time, with a significant improvement of progression-free survival (PFS) and overall survival (OS); and very less side effects in long run. When paired with R-CHOP, Lenalidomide was shown to reduce the unfavourable prognostic effect of the non-GCB phenotype [10]. The goal of this trial, however, was to compare the safety and effectiveness of treating DLBCL with Lenalidomide vs Lenalidomide with R-CHOP.

**METHODS**

This study was conducted in line with PRISMA guidelines [11]. A comprehensive literature search was carried out from 15th November 2022 to 25th November 2022. The literature search was conducted through various databases like PubMed, Google scholar, EMBASE, web of science and finally Cochrane database Library. The literature search was done through various MeSH terms of paramount significance given as: “Lenalidomide” OR “Lenalidomide based regimens” OR “R-CHOP” OR “Lenalidomide + R-CHOP” OR “Diffuse large B-cell Lymphoma(DLBCL)”. The clinical trial was also included for validation of this systematic review and search of various trials was done using ClinicalTrials.gov website. The PICO definition of the study is represented in tabulated form given in Table 1. The study selection was done by two potential authors (A.R and M.S.H). The studies selection was done through assessment of relevant titles, abstracts and retrieved references and those not falling under inclusion criteria were excluded. The full text articles retrieved after selection process were than assessed by two independent authors and any dispute among them was solved with the help of third author(S.M).

**RESULTS**

The initial search retrieved about 300 articles of interest. After removing duplicates and irrelevant studies (100), 20 single arm studies depicting the usefulness of Lenalidomide and Lenalidomide + R-CHOP in DLBCL were assessed for eligibility and only 10 studies were included to synthesize our systematic review. The PRISMA flow chart for selection of final 10 studies given shown in Figure 1.
Included and only randomized controlled trials were included as shown in Table 2.

**Table 2: Showing the demographic profile of the studies included in Lenalidomide study group**

<table>
<thead>
<tr>
<th>Authors/year of study</th>
<th>Country of study</th>
<th>Study design</th>
<th>Study population</th>
<th>Patient numbers (N)</th>
<th>Patient age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mondello et al., (2018)[12]</td>
<td>Italy</td>
<td>Retrospective cohort</td>
<td>R/R DLBCL</td>
<td>123</td>
<td>64</td>
</tr>
<tr>
<td>Witzig et al., (2011)[13]</td>
<td>USA</td>
<td>Randomized control trial phase II</td>
<td>DLBCL</td>
<td>108</td>
<td>66</td>
</tr>
<tr>
<td>Wiernik et al., (2008)[14]</td>
<td>USA</td>
<td>Randomized control trial phase II</td>
<td>R/R DLBCL</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>Beylot-Barry et al., (2019)[16]</td>
<td>France</td>
<td>RCT Phase II</td>
<td>R/R DLBCL leg type</td>
<td>19</td>
<td>79</td>
</tr>
</tbody>
</table>

According to Lenalidomide group statistics, overall response rate (ORR) was 30.58%, complete response rate (CR) was 17.73%, and partial response rate (PR) was 12.69%. The average progression free survival in Lenalidomide group was 12.53 months with 26.9 months of follow-up. The disease specific variables of Lenalidomide group are given in Table 3.

**Table 3: Showing the effectiveness of Lenalidomide in DLBCL in terms of ORR, CR, PR, and PFS**

<table>
<thead>
<tr>
<th>Authors/year of study</th>
<th>Regimen</th>
<th>Dose</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>OS</th>
<th>PFS</th>
<th>Follow-Up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mondello et al., (2018)[12]</td>
<td>Lenalidomide</td>
<td>15mg or 25 mg for 21days</td>
<td>46 (37%)</td>
<td>24 (20%)</td>
<td>22 (17%)</td>
<td>73 months (7-127)</td>
<td>34 months (2-108)</td>
<td>54 months</td>
</tr>
<tr>
<td>Witzig et al., (2011)[13]</td>
<td>Lenalidomide</td>
<td>25mg for 21 days</td>
<td>30 (28%)</td>
<td>8 (7%)</td>
<td>NA</td>
<td>2.7 months</td>
<td>NA</td>
<td>9.2 months</td>
</tr>
<tr>
<td>Wiernik et al., (2008)[14]</td>
<td>Lenalidomide</td>
<td>25mg for 21 days</td>
<td>5 (19%)</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
<td>NA</td>
<td>4 months (0-14.9)</td>
<td>3.7 months</td>
</tr>
</tbody>
</table>

According to Lenalidomide + R-CHOP group statistics, overall response rate (ORR) was 92.89%, complete response rate (CR) was 80.20%, and partial response rate (PR) was 12.69%. The average progression free survival in Lenalidomide + R-CHOP group was 23.6 months with 26.9 months of follow-up. The disease specific variables of Lenalidomide + R-CHOP group are given in Table 4.

**Table 4: Showing the demographic characteristics of the studies included in Lenalidomide + R-CHOP study group**

<table>
<thead>
<tr>
<th>Authors/year of study</th>
<th>Regimen</th>
<th>Dose</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>OS</th>
<th>PFS</th>
<th>Follow-Up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanjai et al., (2021)[17]</td>
<td>USA</td>
<td>Randomized controlled trial Phase II</td>
<td>DLBCL</td>
<td>19 (27.5%)</td>
<td>9 (19.6%)</td>
<td>9 (17.6%)</td>
<td>7.75 months</td>
<td>3.4 months</td>
</tr>
<tr>
<td>Nowakowski et al., (2015)[18]</td>
<td>USA</td>
<td>Randomized controlled trial Phase II</td>
<td>DLBCL</td>
<td>25mg or 21 days</td>
<td>5 (26.3%)</td>
<td>4 (21%)</td>
<td>3.7 months</td>
<td>4.9 months</td>
</tr>
<tr>
<td>Nowakowski et al., (2011)[19]</td>
<td>USA</td>
<td>Randomized controlled trial Phase I</td>
<td>DLBCL</td>
<td>25mg or 21 days</td>
<td>5 (26.3%)</td>
<td>4 (21%)</td>
<td>2 years=45</td>
<td>2 years=39</td>
</tr>
<tr>
<td>Chiappella et al., (2013)[21]</td>
<td>Italy</td>
<td>Randomized controlled trial Phase I</td>
<td>DLBCL</td>
<td>25mg or 21 days</td>
<td>5 (26.3%)</td>
<td>4 (21%)</td>
<td>2 years=45</td>
<td>2 years=39</td>
</tr>
</tbody>
</table>

According to cumulative comparative effectiveness analysis, the Lenalidomide in combination with R-CHOP was a favourable choice in terms of overall response rate, complete response rate, however; partial response rate was better in Lenalidomide group as compared to Lenalidomide + R-CHOP as shown in Figure 2.
b): Safety profile of Lenalidomide and Lenalidomide + R-CHOP study groups

In safety analysis between Lenalidomide and Lenalidomide + R-CHOP group, the combination therapy was associated with increased risk of Hematological and Non-hematological adverse events of grade 3 and more. The events of Hematological toxicities in both groups are given in the figure 3, which is clearly depicting the greater association of hematological toxicities with Lenalidomide + R-CHOP group as given in Table 6.

**Table 6: Showing the safety profile of both Lenalidomide and Lenalidomide + R-CHOP study groups**

<table>
<thead>
<tr>
<th>Author Name (Lenalidomide)</th>
<th>≥ Grade 3 Hematological Toxicity N (%)</th>
<th>≥ Grade 3 Non-Hematological Toxicity N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mondello et al., (2016) [12]</td>
<td>Neutropenia=28(24%), Thrombocytopenia=13(11%)</td>
<td>Elevated transaminases=2(2%), Neuropathy=1(1%)</td>
</tr>
<tr>
<td>Witzig et al., (2011) [13]</td>
<td>Anemia=10(9.2%), Neutropenia=44 (41%), Leukopenia=8 (7.3%), Thrombocytopenia=23 (18.4%)</td>
<td>Dyspnoea=6 (5.5%), Abdominal pain=4 (4%), Pneumonia=3 (3.3%), Deep venous thrombosis=2 (1.6%)</td>
</tr>
<tr>
<td>Wiernik et al., (2008) [14]</td>
<td>Anemia=2(6.1%), Neutropenia=9 (33%), Leukopenia=4 (14.3%), Thrombocytopenia=5 (19%)</td>
<td>Fatigue=2 (6.1%), Pain=1 (4%), Pneumonia=1 (4%), Rash=1 (4%), Fever=2 (6%)</td>
</tr>
<tr>
<td>Czuczman et al., (2017) [15]</td>
<td>Anemia=17 (33%), Neutropenia=22 (43%), Thrombocytopenia=12 (24%)</td>
<td>Respiratory dysfunction=28 (54%), Gastrointestinal dysfunction=37 (72%)</td>
</tr>
<tr>
<td>Beylot-Barry et al., (2019) [16]</td>
<td>Neutropenia=4 (21%), Thrombocytopenia=2 (10%), Lymphopenia=1 (5%)</td>
<td>Atrial fibrillation=3 (10.5%), Skin rash=1 (5%), Sepsis=1 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author Name (Lenalidomide + R-CHOP)</th>
<th>≥ Grade 3 Hematological Toxicity N (%)</th>
<th>≥ Grade 3 Non-Hematological Toxicity N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanjal et al., (2021) [17]</td>
<td>Neutropenia=27 (82%), Thrombocytopenia=16 (48%), Anemia=7 (21%)</td>
<td>Fatigue=10 (30.3%), Sensory neuropathy=4 (12%), Alopecia=24 (73%)</td>
</tr>
<tr>
<td>Nowakowski et al., (2018) [18]</td>
<td>Neutropenia=56 (87.5%), Leukopenia=51 (80%), Thrombocytopenia=28 (44%)</td>
<td>Fatigue=2 (3.1%), sepsis=1 (2%), Pneumonia=2 (3.1%)</td>
</tr>
<tr>
<td>Nowakowski et al., (2016) [19]</td>
<td>Anemia=6 (21%)</td>
<td>Infection=4 (17%), Neurological dysfunction=2 (8.3%), Vascular dysfunction=2 (8.3%)</td>
</tr>
<tr>
<td>Vitolo et al., (2014) [20]</td>
<td>Anemia=10 (20%), Neutropenia=34 (68%), Leukopenia=29 (59%), Thrombocytopenia=15 (30%)</td>
<td>Cardiac dysfunction=1 (2%), Cardiac dysfunction=2 (4%), Skinfish=2 (2%), Deep venous thrombosis=2 (4%)</td>
</tr>
<tr>
<td>Chiappella et al., (2013) [21]</td>
<td>Neutropenia=6 (28%), Thrombocytopenia=2 (9%), Leukopenia=4 (21%)</td>
<td>Cardiac dysfunction=2 (10%), Gastrointestinal dysfunction=1 (5%), Cardiac dysfunction=2 (10%)</td>
</tr>
</tbody>
</table>

**Figure 3:** Showing the association of Hematological adverse events following Lenalidomide vs Lenalidomide + R-CHOP regimen

**DISCUSSION**

DLBCL is a complex illness with many subgroups that respond differently to treatment [22]. Despite conventional R-CHOP therapy, around one-third of DLBCL patients may have disease recurrence or progression, emphasizing the need for additional effective therapies [23]. Lenalidomide is an immunomodulatory medication that has been proven to be effective in DLBCL as a monotherapy as well as in combination therapy [24]. Several trials have investigated Lenalidomide monotherapy for relapsed or refractory DLBCL, with
response rates varying between observed range of 24% to 36% [14, 18]. In a phase II trial of Lenalidomide in relapsed or refractory DLBCL, 25 patients were treated with Lenalidomide 25 mg/day on days 1-21 of a 28-day cycle [14]. The ORR was 36%, with a CR rate of 8%. The median PFS was 3.1 months, while the median overall survival (OS) was 7.3 months. In another phase II research of Lenalidomide in relapsed or refractory DLBCL, 46 patients were treated with Lenalidomide 25 mg/day on days 1-21 of a 28-day cycle [25]. The ORR was 24%, with a CR rate of 6.5%. The observed median PFS was 2.6 months, and the median OS was 7.6 months. According to these findings, Lenalidomide monotherapy shows limited effectiveness in relapsed or refractory DLBCL. These findings were consistent with our research findings, which showed that monotherapy was less successful than combination treatment. The ORR in our research was 30.56%, with a CR rate of 12.53%, which was comparable to other studies' findings. Several clinical trials have evaluated the efficacy and safety of Lenalidomide plus R-CHOP in newly diagnosed DLBCL [13]. In a phase II trial of Lenalidomide + R-CHOP in elderly individuals with DLBCL, 47 patients were given 15 mg/day of Lenalidomide plus R-CHOP on days 1-14 of a 21-day cycle [13]. The ORR was 93%, with a 72% CR rate. The two-year PFS was 75% and the two-year OS was 83%. In a phase II trial of Lenalidomide + R-CHOP in DLBCL, 59 patients were given 15 mg/day of Lenalidomide plus R-CHOP on days 1-14 of a 21-day cycle [20]. The ORR was 88%, with a CR rate of 56%, 2-year PFS was 61%, and the 2-year OS was 78%. In a phase III study of Lenalidomide plus R-CHOP in DLBCL, 233 patients were randomized to receive R-CHOP with or without Lenalidomide [26]. In this particular study, the ORR in Lenalidomide + R-CHOP was 66%, complete response 59% and partial response of 7%. These research findings corroborated what we had observed. The ORR in our trial for Lenalidomide + R-CHOP was 92.89%, with a complete response of 80.20% and a partial response of 12.69%. The most prevalent type of aggressive NHL is DLBCL. Lenalidomide, an immunomodulatory medication, has been demonstrated to be effective as monotherapy in patients with recurrent or refractory DLBCL [27]. However, its safety in combination with R-CHOP is unknown. In a phase 3 clinical trial (ROBUST), the safety and efficacy of Lenalidomide plus R-CHOP in DLBCL patients were assessed. The study enrolled 818 patients who were randomly assigned to either R-CHOP + Lenalidomide (n=410) or R-CHOP plus placebo (n=408). The primary endpoint of event-free survival (EFS) was not attained, and there was no statistically significant difference in overall survival (OS) between the two groups. The addition of Lenalidomide, on the other hand, was linked with a higher incidence of grade 3 or 4 neutropenia (76.8% vs 55.4%), febrile neutropenia (13.3% vs 7.1%), and thrombocytopenia (15.3% vs 7.1%). In addition, the Lenalidomide group had a greater rate of treatment termination due to adverse events (23.2% vs 12.0%) [27]. Our research's safety trend was consistent with the previously described study, with neutropenia being the most often seen haematological toxicity, followed by thrombocytopenia. Another phase II trial investigated Lenalidomide in conjunction with R-CHOP in elderly individuals with untreated DLBCL [20]. The trial included 49 patients, and the findings revealed that the safety profile was good, with no paramount increase in side effects as compared to R-CHOP alone. Hematologic toxicity, particularly neutropenia and thrombocytopenia, was the most prevalent adverse event [20]. Finally, in DLBCL patients, the use of Lenalidomide with R-CHOP combination may increase the risk of hematologic toxicity and therapy abandonment due to adverse events. Careful monitoring and dosage modification may be necessary to reduce toxicity. Individual patient safety profiles for Lenalidomide + R-CHOP should be studied, taking the patient's age, comorbidities, and baseline hematologic characteristics into account.

CONCLUSIONS

DLBCL is an aggressive type of NHL. The two therapy options (Lenalidomide and Lenalidomide + R-CHOP) were compared in this study. In conclusion, the combination therapy was found to be successful in terms of greater ORR and CR, while the partial response rate was equivalent between the two groups. The safety profile revealed that combination therapy was associated with haematological and non-haematological side effects, most notably neutropenia and thrombocytopenia.

Authors Contribution

Conceptualization: MSA, SM, AR1, AR2
Methodology: SY, MAKK
Formal Analysis: MF, MFB
Writing-review and editing: MSA, SM, AR1, SY, MAKK, MF, MFB

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

REFERENCES


PJHS VOL. 4 Issue. 8 August 2023

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DOI: https://doi.org/10.54393/pjhs.v4i08.947


[19] Nowakowski GS, LaPlant B, Habermann TM, Rivera


