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Systematic Review

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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ABSTRACT

The most frequent cause of non-Hodgkin lymphoma, which accounts for around one-third of cases, is diffuse large B cell lymphoma (DLBCL). Immune chemotherapy combined with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard therapy for DLBCL. **Objective:** To analysing the utilization of Lenalidomide versus Lenalidomide R-CHOP regimen in treatment of DLBCL in terms of treatment efficacy and safety. **Methods:** PRISMA guidelines were followed for conducting this study. A thorough literature search was done from November 15 to November 25, 2022. A variety of databases, including PubMed, Google Scholar, and other, were used to conduct the literature search. Finally, for this systematic review, 10 studies were chosen. **Results:** In our study the monotherapy with Lenalidomide was found less significant in terms of improvement in Overall response rate, complete response among patients with DLBCL. However; Lenalidomide + R-CHOP was more effective in improving overall response rate (ORR) with ORR of 92.89% vs 30.58% and complete response rate (CRR) of 80.20% vs 12.53%. The partial response rate (PR) was comparable between two therapies. similarly, the Progression free survival was also better in combination therapy. Haematological and Non-Hematological adverse effects of grade >3 were found higher among patients with combination therapy and Neutropenia was commonly observed adverse effect. **Conclusions:** Combination therapy was associated with significant improvement in disease outcome, however; the adverse effects were reported high in combination therapy vs monotherapy.

INTRODUCTION

Non-Hodgkin lymphomas (NHL) are classified into numerous subtypes, with the aggressive diffuse large B-cell lymphoma (DLCBL) being the most frequent [1]. DLCBL 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 germinal centres, 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.

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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).

Table 1: Showing the PICO definition of the study

Population	Patients with diagnosed DLBCL
Intervention	Lenalidomide based monotherapy
Comparator	Lenalidomide + R-CHOP based combination therapy
Outcomes	Overall response rate, Complete response, Partial response and Progression free survival.

The standard variables of interest like author name, year of study, country of study, mean age of the patients, and study type were extracted in first place than disease specific variables of interest like disease characteristics, type of regimen given, follow-up duration, complete response (CR), partial response (PR), overall response rate (ORR), progression free survival (PFS) and finally adverse events either Haematological or Non-Haematological and >grade 3 events were extracted. The randomised controlled trials quality assessment was done through Jadad scale (11). The risk of bias was clearly identified and studies with best methodologies were opted for analysis. Data analysis were done through SPSS. V. 25, because all variables were just expressed in the form of frequency and %ages due to qualitative nature of the variables and similarly quantitative variables were expressed as mean and standard deviation, so no correlation statistics were performed.

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.

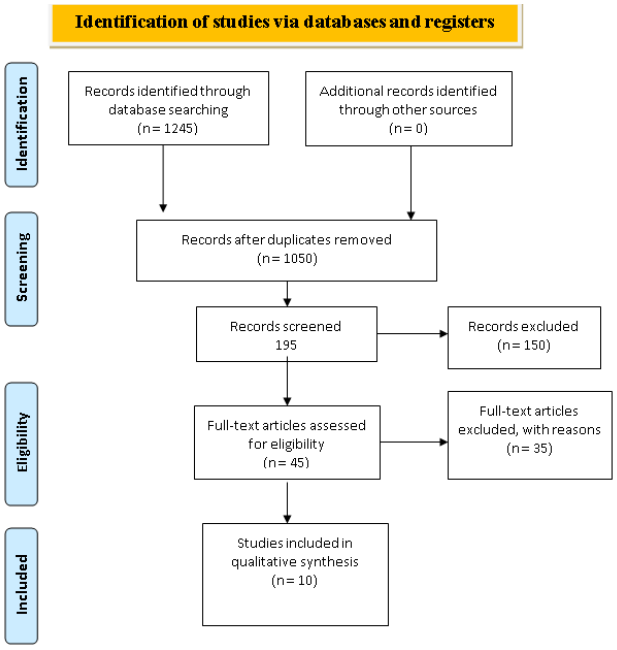

Figure 1: PRISMA flow chart of the selected studies included in systematic review

a): Efficacy profile of Lenalidomide and Lenalidomide + R-CHOP study groups:

A total of 327 patients were included in Lenalidomide study group and the mean age of the patients in Lenalidomide study group was 68.6±17.3 years. Patients with DLBCL were

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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

Authors/year of study	Country of study	Study design	Study population	Patient numbers (N)	Patient age
Mondello *et al.*, (2016) [12]	Italy	Retrospective cohort	R/R DLBCL	123	64
Witzig *et al.*, (2011) [13].	USA	Randomized control trial phase II	DLBCL	108	66
Wiernik *et al.*, (2008) [14].	USA	Randomized control trial phase II	R/R DLBCL	26	65
Czuczman *et al.*, (2017) [15].	Multi-centre	RCT Phase II/III	R/R DLBCL	51	69
Beylot-Barry *et al.*, (2019) [16].	France	RCT Phase II	R/R DLBCL leg type	19	79

According to Lenalidomide group statistics, overall response rate (ORR) was 30.58%, complete response rate (CRR) was 12.53% and partial response rate (PRR) was 17.73%. The average progression free survival in Lenalidomide group was 9.8 months with 23.5 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

Authors/year of study	Regimen	Dose	ORR	CR	PR	OS	PFS	Follow-Up time
Mondello *et al.*, (2016) [12]	Lenali-domide	15mg or 25 mg for 21days	46 (37 %)	21 (17 %)	24 (20 %)	73 months (7-127)	34 months (2-108)	54 months
Witzig *et al.*, (2011) [13].	Lenali-domide	25mg for 21 days	30 (28 %)	8 (7 %)	22 (20 %)	NA	2.7 months	9.2 months
Wiernik *et al.*, (2008) [14].	Lenali-domide	25mg for 21 days	5 (19 %)	3 (12 %)	2 (8 %)	NA	4 months (0-14.5)	3.7 months
Czuczman *et al.*, (2017) [15].	Lenali-domide	10mg or 25 mg for 21days	14 (27.5 %)	5 (9.8 %)	9 (17.6 %)	7.75 months	3.4 months	1.84 months
Beylot-Barry *et al.*, (2019) [16].	Lenali-domide	25mg for 21 days	5 (26.3 %)	4 (21 %)	1 (5.3 %)	19.4 months	4.9 months	49 months

A total of 197 patients were included in Lenalidomide + R-CHOP study group and the mean age of the patients in Lenalidomide study group was 66 ± 12.2 years. Patients with diffuse large B-cell lymphoma were included and only randomized controlled trials were included as shown in (Table 4).

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

Authors/year of study	Country of study	Study design	Study population	Patient numbers (N)	Patient age
Sanjal et al., (2021) [17].	USA	Randomized controlled trial Phase II	DLBCL	39	63
Nowakowski et al., (2015) [18].	USA	Randomized controlled trial Phase II	DLBCL	64	65
Nowakowski et al., (2011) [19].	USA	Randomized controlled trial Phase I	DLBCL	24	65
Vitolo et al., (2014) [20].	Italy	Randomized controlled trial Phase II	DLBCL	49	69
Chiappella et al., (2013) [21].	Italy	Randomized controlled trial Phase I	DLBCL	21	68

According to Lenalidomide + R-CHOP group statistics, overall response rate (ORR) was 92.89%, complete response rate (CRR) was 80.20% and partial response rate (PRR) 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 5).

Table 5: Showing the effectiveness of Lenalidomide + R-CHOP in DLBCL in terms of ORR, CR, PR, and PFS

Authors/year of study	Regimen	Dose	ORR	CR	PR	OS	PFS	Follow-Up time
Sanjal et al., (2021) [17].	Lenalidomide + R-CHOP	Lenalidomide: 25mg, Rituximab: 375mg/m^2, Cyclophosphamide: 750mg/m^2, Vincristine: 1.4mg/m^2, prednisone: 100mg	32 (97%)	29 (88%)	3 (9.0%)	24 months	24 months	52 months
Nowakowski et al., (2015) [18].	Lenalidomide + R-CHOP	Lenalidomide: 25mg, Rituximab: 375mg/m^2, Cyclophosphamide: 750mg/m^2, Vincristine: 1.4mg/m^2, prednisone: 100mg	63 (98%)	51 (80%)	12 (18.7%)	70 months	37 months	23.5 months
Nowakowski et al., (2011) [19].	Lenalidomide + R-CHOP	Lenalidomide: 25mg, Rituximab: 375mg/m^2, Cyclophosphamide: 750mg/m^2, Vincristine: 1.4mg/m^2, prednisone: 100mg	24 (100%)	19 (77%)	5 (20.8%)	NA	NA	7 months
Vitolo et al., (2014) [20].	Lenalidomide + R-CHOP	Lenalidomide: 25mg, Rituximab: 375mg/m^2, Cyclophosphamide: 750mg/m^2, Vincristine: 1.4mg/m^2, prednisone: 40mg	45 (92%)	42 (86%)	3 (6%)	2 years=45	2 years=39	28 months
Chiappella et al., (2013) [21].	Lenalidomide + R-CHOP	Lenalidomide: 25mg, Rituximab: 375mg/m^2, Cyclophosphamide: 750mg/m^2, Vincristine: 1.4mg/m^2, prednisone: 100mg	19 (90%)	17 (81%)	2 (9%)	NA	NA	<24 months

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).

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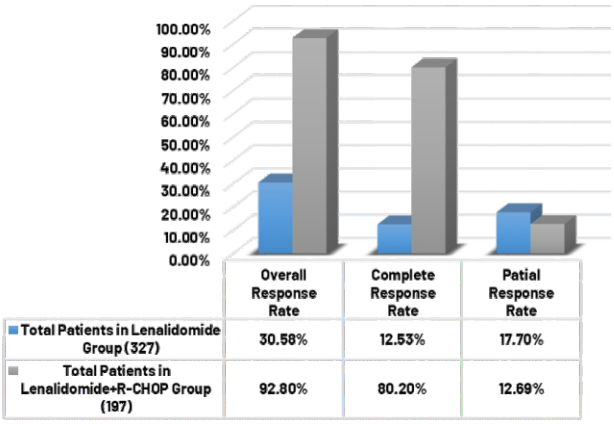

Figure 2: Showing the cumulative comparative effectiveness results of both Lenalidomide and Lenalidomide + R-CHOP study groups

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

Author Name (Lenalidomide)	≥ Grade 3 Hematological Toxicity N (%)	≥ Grade 3 Non-Hematological Toxicity N (%)
Mondello et al., (2016) [12]	Neutropenia=29(24%), Thrombocytopenia=13(11%)	Elevated transaminases=2(2%), Neuropathy=1(1%).
Witzig et al., (2011) [13].	Anemia=10 (9.2%), Neutropenia=44 (41%), Leukopenia=8 (7.3%), Thrombocytopenia=21(19.4%)	Dyspnoea=6 (5.5%), Abdominal pain=4 (4%), Pneumonia= 3 (3.3%), Deep venous thrombosis=2 (2.3%).
Wiernik et al., (2008) [14].	Anemia=2 (6.1%), Neutropenia=9 (33%), Leukopenia=4 (14.3%), Thrombocytopenia=5 (20%) Lymphopenia=1 (4%)	Fatigue=2(6.1%), Pain=1 (4%), Pneumonia=1 (4%), Rash=1 (4%), Fever=2 (6%)
Czuczman et al., (2017) [15].	Anemia=17 (33%), Neutropenia=22 (43%), Thrombocytopenia=12 (24%)	Respiratory dysfunction=28 (54%), Gastrointestinal dysfunction=37 (72%)
Beylot-Barry et al., (2019) [16].	Neutropenia=4 (21%), Thrombocytopenia=2 (10%) Lymphopenia=1 (5%)	Atrial fibrillation=3 (10.5%), Skin rash=1 (5%), Sepsis=1 (5%)
Author Name (Lenalidomide + R-CHOP)	**≥ Grade 3 Hematological Toxicity N (%)**	**≥ Grade 3 Non-Hematological Toxicity N (%)**
Sanjal et al., (2021) [17].	Neutropenia=27(82%), Thrombocytopenia=16(48%), Anemia=7(21%).	Fatigue=10(30.3%), Sensory neuropathy=4(12%), Alopecia=24(73%)
Nowakowski et al., (2015) [18].	Neutropenia=56 (87.5%), Leukopenia=51 (80%), Thrombocytopenia=28 (44%)	Fatigue=2 (3.1%), sepsis=1 (2%), Pneumonia=2 (3.1%).
Nowakowski et al., (2011) [19].	Anemia=5 (21%)	Infection=4 (17%), Neurological dysfunction=2 (8.3%), Vascular dysfunction=2 (8.3%).
Vitolo et al., (2014) [20].	Anemia=10 (20%), Neutropenia=34 (69%), Leukopenia=29 (59%), Thrombocytopenia=15 (30%)	Cardiac dysfunction=1 (2%), Cardiac dysfunction=2 (4%), Skin rash=1 (2%), Deep venous thrombosis=2 (4%)
Chiappella et al., (2013) [21].	Neutropenia=6 (28%), Thrombocytopenia=2 (9%), Leukopenia=4 (21%)	Cardiac dysfunction=2 (10%) Gastrointestinal dysfunction=1 (5%), Cardiac dysfunction=2 (10%)

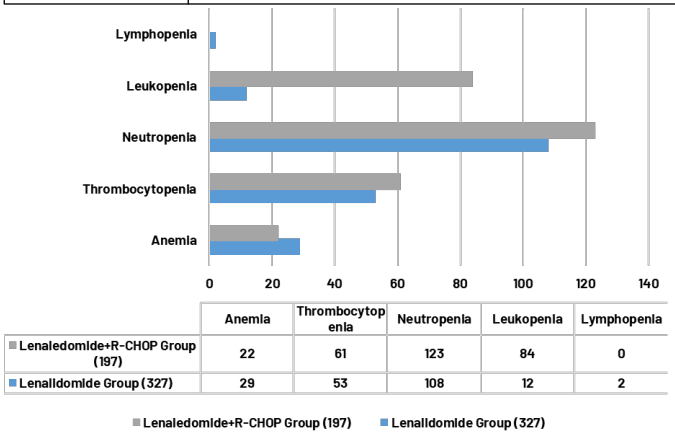

Figure 3: Showing the association of Hematological adverse events following Lenalidomide vs Lenalidomide + R-CHOP regimen

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

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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 30.58 %, 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 % versus 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 2 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:
Methodology:
Formal Analysis:
Writing-review and editing:

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

Conflicts of Interest

The authors declare no conflict of interest.

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