Efficacy and Safety of Lenalidomide Monotherapy for Relapsed/Refractory Diffuse Large B Cell Lymphoma: Systematic Review and Meta-Analysis

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Introduction: Several maintenance therapies are available for treatment of patients with relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL). The objective of this review was to assess the efficacy and safety of lenalidomide monotherapy in these patients.

Methods: MEDLINE, EMBASE, and the Cochrane Library databases were searched for publications up to April 7, 2021. Original studies that had information on lenalidomide monotherapy for DLBCL patients with R/R status were included. Meta-analyses of response rates, adverse events (AEs), overall survival (OS), and progression-free survival (PFS) were performed. The pooled event rates were calculated using a double arcsine transformation to stabilize the variances of the original proportions. Subgroup analysis was used to compare patients with different germinal center B-cell-like (GCB) phenotypes.

Results: We included 11 publications that examined DLBCL patients with R/R status. These studies were published from 2008 to 2020. The cumulative objective response rate (ORR) for lenalidomide monotherapy was 0.33 (95% CI: 0.26, 0.40), and the ORR was better in patients with the non-GCB phenotype (0.50; 95% CI: 0.26, 0.74) than the GCB phenotype (0.06; 95% CI: 0.03, 0.11). The major serious treatment-related AEs were neutropenia, thrombocytopenia, respiratory disorders, anemia, and diarrhea. The median PFS ranged from 2.6 to 34 months and the median OS ranged from 7.8 to 37 months.

Conclusion: This study provides evidence that lenalidomide monotherapy was active and tolerable in DLBCL patients with R/R status. Patients in the non-GCB subgroup had better responsiveness.

Keywords: diffuse large B-cell lymphoma, lenalidomide, monotherapy, treatment outcome, systematic review, meta-analysis
INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) and accounts for about 40% of all diagnosed lymphomas (1). The current standard first-line treatment of DLBCL is immunochemotherapy with rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone, a regimen that provides complete and sustained remission for about 75% of newly diagnosed patients (2). The remaining patients are classified as having “relapsed” DLBCL if there is any new lesion after complete response (CR), and as “refractory” DLBCL if 50% or more of the lesions increased in size following initial treatment or if there is appearance of a new lesion during or following the initial treatment (3).

For DLBCL patients with relapsed/refractory (R/R) disease, the standard therapeutic option for those who are chemosensitive to second-line regimens is high-dose therapy plus autologous stem cell transplantation (ASCT) (4). Patients who are ineligible for ASCT or who fail after second-line treatment typically have poor prognoses. However, recent findings indicated that these patients may benefit from alternative salvage therapies. For example, lenalidomide with tafasitmab is often an effective treatment for DLBCL patients with R/R status.

Lenalidomide is a second-generation immunomodulatory drug, and several clinical trials reported that it provided effective treatment of multiple myeloma, myelodysplastic syndrome, and mantle cell lymphoma (5, 6). Other trials showed that lenalidomide monotherapy was an active and safe treatment for DLBCL patients with R/R status (7, 8). However, there has been no systematic synthesis of available studies on this topic.

The objective of the present study was to assess the efficacy and safety of lenalidomide monotherapy for DLBCL patients with R/R status and provide useful guidance for the treatment of these patients in clinical settings.

MATERIALS AND METHODS

Search Strategy

The present systematic review and meta-analysis followed the PRISMA statement (9, 10) and used searches from Embase, Medline, and the Cochrane library to identify articles published up to April 7, 2021 (Figure 1). The search terms included “lenalidomide”, “diffuse large B-cell lymphoma”, and “lymphoma”, and appropriate search strategies and syntax were used for each database (Appendix I).

Selection Criteria and Study Selection

The criteria for inclusion/exclusion were as follows: (i) studies were included if they were original randomized clinical trials, prospective cohort studies, prospective one-arm studies, or observational studies, but excluded if they were letters, commentaries, conference abstracts, case reports, case series, preclinical trials, review articles, or meta-analyses; (ii) studies were included if they examined populations of DLBCL patients with R/R status; (iii) studies were included if they provided information on lenalidomide monotherapy; and (iv) studies were included if they provided information on the outcomes of response rate, safety events, and survival [overall survival (OS) and progression-free survival (PFS)].

The titles and abstracts were first independently screened by two authors (Ou Bai and Jia Li) to identify potentially eligible publications. Then, full-text screening was independently performed by Wei Guo and Jia Li. Disagreements were resolved by discussion or by referral to a third party.

Data Collection

Jia Li, Xingtong Wang, and Yangzhi Zhao performed the data collection independently and resolved disagreements by discussion or referral to a third party. The basic information of the included studies was study design; publication year; patient demographics; and data on response rates, safety events, and survival (OS and PFS). Responses were determined using the Cheson criteria, and included ORR, CR, partial response (PR), stable disease (SD), and progressive disease (PD) (3). PFS was defined as the time from the onset of lenalidomide monotherapy until PD (defined by RECIST criteria ver. 1.1) (11). OS time was defined as the time from the onset of lenalidomide monotherapy until death. Adverse events were reported and graded according to CTCAE ver. 5.0 (12).

Data Analysis

Because the target was the efficacy and safety of the one-arm intervention, not a comparison of groups, the risk of bias assessment was performed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (13). Meta-analyses of response rates, safety events, and survival rates (OS and PFS) were performed. Sensitivity analyses were not performed due to the limited amount of data. The pooled event rates were calculated using a double arcsine transformation to stabilize the variances of the original proportions. Each pooled rate is presented as proportion with a 95% confidential interval (CI). Heterogeneity was estimated using the Q-test. When the P-value was less than 0.1 (Q-test) and the I² was greater than 50%, the result was considered heterogeneous, and a random-effects model was used for analysis; otherwise, a fixed-effects model was used. Subgroup analysis was performed to examine patients with germinal center B-cell-like (GCB) phenotype and non-GCB phenotype. A P-value below 0.05 was considered significant. All statistical analyses were performed using Stata version 15.0 (Stata Corp. Texas, USA).

RESULTS

Basic Characteristics of Studies

Our initial screening led to the identification of 1237 potentially eligible studies (1231 from PubMed, EMBASE, and Cochrane Library, and 6 from other sources). We ultimately excluded 1226 of these studies based on the inclusion and exclusion criteria, and
included 11 publications from 10 studies from that were published from 2008 to 2020 (Figure 1 and Table 1) (7, 8, 14–22). Five of these studies were prospective one-arm studies (7, 8, 15, 16, 20, 21), four were retrospective analyses (14, 17, 18, 22), and one was a randomized controlled trial (19). The sample size ranged from 15 to 153 patients, and the median patient age ranged from 51 to 79 years old. Based on the ROBINS-I tool, the included studies had variable quality (Table 2). Moreover, because these data were from one-arm interventions, each study had a high risk of confounding. We also classified six studies as having problems with selection bias. The one RCT, in which our extracted data were targeted as a one-arm treatment, also had a high risk of confounding.

Response Rates and Adverse Events
All publications reported ORRs, and the pooled results had an ORR of 0.33 (95% CI: 0.26, 0.40, I^2 = 59.55%; Figure 2A). Among all 600 patients, 197 achieved at least PR. The cumulative CR (which included confirmed and unconfirmed CR) was 0.16 (95% CI: 0.11, 0.21, I^2 = 56.40%; Figure 2B). PD was present in about half the patients, and the cumulative PD was 0.46 (95% CI: 0.39, 0.54, I^2 = 63.18%; Figure 2C). We also determined several other responses (Table 3). Notably, the median response duration ranged from 4.1 months to 18.5 months (Table 4).

We performed subgroup analysis to compare the responses of patients with the GCB and non-GCB phenotypes (Table 5,
# TABLE 1 | Characteristics of included publications.

**Wiernik et al. (8)**

| Design | Single-arm, multicenter, open-label, phase II study in USA from August 2005 to September 2006 |
| Patient population | Relapsed/refractory aggressive NHL |
| Overall sample | 49 patients with relapsed/refractory aggressive NHL, 26 patients with DLBCL |
| Age (years), median (range) | Whole cohort: 65 (23, 86) Patients with DLBCL: Not specified |
| Male, n/N (%) | Whole cohort: 25/49 (51.0) Patients with DLBCL: Not specified |
| Baseline characteristics | IPI score, n/N (%) |
| | Whole cohort | Patients with DLBCL |
| 0–1 | 8/49 (16.3) | Not specified |
| 2–3 | 35/49 (71.4) | Not specified |
| 4–5 | 6/49 (12.2) | Not specified |
| ECOG performance status, n/N (%) | Not specified |
| ISS disease stage, n/N (%) | Not specified |
| Median number of prior treatment regimens | 4 |
| Patients with GCB | Not specified |

**Maintenance therapy**

Oral lenalidomide (25 mg once daily) on days 1 to 21 of every 28-day cycle. Patients continued therapy for 52 weeks as tolerated or until disease progression.

**Outcomes**

Response and safety

**Hernandez-Ilizaliturri et al. (14)**

| Design | Retrospective one-arm study that reviewed data in USA for an unspecified period |
| Patient population | Relapsed/refractory DLBCL |
| Overall sample | 40 overall, 23 with GCB, 17 with non-GCB |
| Age (years), median (range) | Whole cohort: 66 (43, 80) GCB: 65 (46, 73) Non-GCB: 68 (43-80) |
| Male, n/N (%) | Whole cohort: 24/40 (60.0) GCB: 13/23 (56.5) Non-GCB: 11/17 (64.7) |
| Baseline characteristics | IPI score, n/N (%) |
| | Whole cohort | GCB | Non-GCB |
| 0–1 | 11/40 (27.5) GCB: 8/23 (34.8) Non-GCB: 3/17 (17.6) |
| 2–3 | 17/40 (42.5) GCB: 10/23 (43.5) Non-GCB: 7/17 (41.2) |
| 4–5 | 12/40 (30.0) GCB: 5/23 (21.7) Non-GCB: 7/17 (41.2) |
| ECOG performance status, n/N (%) | Not specified |
| ISS disease stage, n/N (%) | Whole cohort: GCB: Non-GCB |
| I | 4/40 (10.0) GCB: 3/23 (13.0) Non-GCB: 1/17 (5.9) |
| II | 4/40 (10.0) GCB: 3/23 (13.0) Non-GCB: 1/17 (5.9) |
| III | 12/40 (30.0) GCB: 8/23 (34.8) Non-GCB: 4/17 (23.5) |
| IV | 20/40 (50.0) GCB: 9/23 (39.1) Non-GCB: 11/17 (64.7) |
| Median number of prior treatment regimens | Whole cohort: GCB: Non-GCB |
| 4 (2, 13) GCB: 4 (2, 7) Non-GCB: 4 (2, 13) |
| Patients with GCB, n/N (%) | 23/40 (57.5) |

**Maintenance therapy**

All 40 patients in the final analysis received single-agent lenalidomide (25 mg once daily) for 21 days of a 28-day cycle. Patients continued lenalidomide until disease progression or unacceptable toxicity.

(Continued)
### TABLE 1 | Continued

| Outcomes | Response and survival outcomes |
|----------|--------------------------------|
| **Witzig et al.** (15) | Single-arm, multicenter, open-label, phase II study in USA from November 2006 to March 2008 |
| **Patient population** | Relapsed/refractory aggressive NHL |
| **Overall sample** | 217 patients with relapsed/refractory aggressive NHL, and 108 patients with DLBCL |
| **Age (years), median (range)** | Whole cohort 66 (21, 87) Patients with DLBCL Not specified. |
| **Male, n/N (%)** | Whole cohort 140/217 (64.5) Patients with DLBCL Not specified. |
| **Baseline characteristics** | IPI score, n/N (%) Whole cohort 0–1 44/217 (20.3) Patients with DLBCL Not specified. 2–3 136/217 (62.7) Not specified. 4–5 37/217 (17.1) Not specified. |
| | ECOG performance status, n/N (%) Whole cohort 0 90/217 (41.5) Patients with DLBCL Not specified. 1 100/217 (46.1) Not specified. |
| | ISS disease stage, n/N (%) Not specified. |
| | Median number of prior treatment regimens (range) Patients with GCB, n/N (%) Not specified. 3 (1, 13) |
| **Maintenance therapy** | Oral lenalidomide (25 mg once daily) on days 1 to 21 of every 28-day cycle until disease progression or unacceptable adverse events |
| **Outcomes** | Response, safety, and survival |
| **Lakshmaiah et al.** (16) | Prospective one-arm study in India from March 2011 to December 2012 |
| **Patient population** | Relapsed/refractory NHL |
| **Overall sample** | 25 patients with relapsed/refractory aggressive NHL, and 15 patients with DLBCL |
| **Age (years), median (range)** | Whole cohort 51 Patients with DLBCL Not specified. |
| **Male, n/N (%)** | Whole cohort 140/217 (64.5) Patients with DLBCL Not specified. |
| **Baseline characteristics** | IPI score, n/N (%) Not specified. |
| | ECOG performance status, n/N (%) Not specified. |
| | ISS disease stage, n/N (%) Not specified. |
| | Median number of prior treatment regimens Patients with GCB, n/N (%) Not specified. |
| **Maintenance therapy** | Oral lenalidomide (starting at 20 mg/day and adjusted based on tolerability) from day 1 to 21 of every 28-day cycle until disease progression or unacceptable adverse events |
| **Outcomes** | Response, safety, and survival |
| **Zinzani et al.** (17) | Retrospective one-arm study that reviewed data in Italy from April 2008 to November 2010 |
| **Patient population** | Relapsed/refractory aggressive NHL |
| **Overall sample** | 64 patients with relapsed/refractory aggressive NHL and 19 patients with DLBCL |
| **Age (years), median (range)** | Whole cohort 71 (44, 84) Patients with DLBCL Not specified. |

(Continued)
TABLE 1 | Continued

Male, n/N (%) | Whole cohort 43/71 (67.2) | Patients with DLBCL Not specified.

Baseline characteristics
IPI score, n/N (%) | Not specified.
ECOG performance status, n/N (%) | Not specified.
ISS disease stage, n/N (%) | Not specified.
Median number of prior treatment regimens | 3 (1, 17)

Maintenance therapy
Lenalidomide monotherapy with unspecified details.

Outcomes
Response, safety, and survival

Mondello et al. (18)
Design
Retrospective one-arm study that reviewed data in Italy from January 2006 to January 2015
Patient population
Relapsed/refractory DLBCL
Overall sample
123 overall, 57 with GCB, 66 with non-GCB
Age (years), median
Whole cohort 64
GCB Not specified.
Non-GCB Not specified.

Male, n/N (%) | Whole cohort 75/123 (61.0) | Patients with GCB, n/N (%) Not specified.

Baseline characteristics
IPI score, n/N (%) | Whole cohort 0–1 6/123 (4.9)
2–3 75/123 (61.0)
4–5 42/123 (34.1)

ECOG performance status, n/N (%) | Whole cohort >1 21/123 (17)

ISS disease stage, n/N (%) | Whole cohort I 3/123 (2.4)
II 19/123 (15.4)
III 23/123 (18.7)
IV 78/123 (63.4)

Prior treatment regimens, median (range) | Whole cohort 1 (1, 3)

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Czuczman et al. (19)
Design
Phase II/III multicenter, randomized, open-label international study from 2 September 2010 to 5 April 2018 (DLC-001 trial)
Patient population
Relapsed/refractory DLBCL
Overall sample
51 overall, 23 with GCB, 28 with non-GCB
Age (years), median (range) | Whole cohort 69 (28, 84)
GCB 70 (37, 84)
Non-GCB 68 (28, 78)

Male, n/N (%) | Whole cohort 30/51 (58.8) | Patients with GCB, n/N (%) Not specified.

Baseline characteristics
IPI score, n/N (%) | Not specified.

(Continued)
| TABLE 1 | Continued |
|----------|-----------|
| **ECOG performance status, n/N (%)** | | | |
| 0 | 18/51 (35.3) | 6/23 (26.1) | 12/28 (42.9) |
| 1 | 24/51 (47.1) | 12/23 (52.2) | 12/28 (42.9) |
| 2 | 7/51 (13.7) | 4/23 (17.4) | 3/28 (10.7) |
| **ISS disease stage, n/N (%)** | | | |
| Not specified. | | | |
| **Prior treatment regimens** | Whole cohort | GCB | Non-GCB |
| 1 | 5/51 (9.8) | 2/23 (8.7) | 3/28 (10.7) |
| 2 | 21/51 (41.2) | 7/23 (30.4) | 14/28 (50.0) |
| ≥3 | 25/51 (49.0) | 14/23 (60.9) | 11/28 (39.3) |
| **ASCT** | 13/51 (25) | 6/23 (26.1) | 7/28 (25.0) |
| **Patients with GCB, n/N (%)** | 23/51 (45.1) | | |
| **Maintenance therapy** | Oral daily lenalidomide (25 mg for creatinine clearance ≥ 60 mL/min; 10 mg for creatinine clearance ≥ 30 mL/min and < 60 mL/min) for day 1 to 21 in each 28-day cycle until progressive disease (PD), unacceptable toxicity, or voluntary withdrawal |
| **Outcomes** | **Response, safety, and survival** |
| **Ferreri et al. (20, 21)** | Design | Open label, single-arm, multicenter phase II trial in Italy from 24 March 2009 to 22 December 2015 |
| **Patient population** | Relapsed/refractory DLBCL |
| **Overall sample** | 46 overall, 20 with GCB, and 19 with non-GCB |
| **Age (years), median (range)** | Whole cohort | GCB | Non-GCB |
| | 72 (34, 86) | Not specified. | Not specified. |
| **Male, n/N (%)** | Whole cohort | GCB | Non-GCB |
| | 27/46 (58.7) | Not specified. | Not specified. |
| **Baseline characteristics** | IPI score, n/N (%) | Whole cohort | GCB | Non-GCB |
| | 0–1 | 8/46 (17.4) | Not specified. | Not specified. |
| | 2–3 | 33/46 (71.7) | Not specified. | Not specified. |
| | 4–5 | 5/46 (10.9) | Not specified. | Not specified. |
| **ECOG performance status, n/N (%)** | Whole cohort | GCB | Non-GCB |
| 0 | 29/46 (63.0) | Not specified. | Not specified. |
| 1 | 15/46 (32.6) | Not specified. | Not specified. |
| 2 | 1/46 (2.2) | Not specified. | Not specified. |
| 3 | 1/46 (2.2) | Not specified. | Not specified. |
| **ISS disease stage, n/N (%)** | Advanced stage | Whole cohort | GCB | Non-GCB |
| | 35/46 (76.1) | Not specified. | Not specified. |
| **Prior treatment regimens, median (range)** | Not specified |
| **Patients with GCB, n/N (%)** | 20/39 (51.3) |
| **Maintenance therapy** | Oral lenalidomide (25 mg per day for 21 days every 28 days) started within 2 months from salvage chemotherapy conclusion and until lymphoma progression or unacceptable toxicity (severely compromised organ function, quality of life, or both) |
| **Outcomes** | **Response, safety, and survival** |
| **Beylot-Barry et al. (7)** | Design | Open-label, multicenter, single-arm, two-stage, phase II clinical trial in France from July 2012 to September 2014 |
| **Patient population** | Relapsed/refractory primary cutaneous DLBCL, leg type |
| **Overall sample** | 19 |
| **Age (years), median (range)** | 79 (69, 92) |
| **Male, n/N (%)** | 3/19 (15.8) |
| **Baseline characteristics** | IPI score, n/N (%) | Not specified |
| **ECOG performance status, n/N (%)** | Whole cohort | GCB | Non-GCB |
| 0 | 12/19 (63.2) |
| 1 | 5/19 (26.3) |
| 2 | 2/19 (10.5) |

(Continued)
### TABLE 1 | Continued

| ISS disease stage, n/N (%) | Median number of prior treatment regimens (range) | Patients with GCB, n/N (%) |
|---------------------------|-----------------------------------------------|---------------------------|
| Not specified.            | Not specified.                                |                           |

**Maintenance therapy**

Oral lenalidomide (25 mg once daily) on days 1 to 21 of every 28-day cycle for 12 cycles, as tolerated or until disease progression

**Outcomes**

**Broccoli et al. (22)**

**Design**

Retrospective one-arm study that reviewed data in Italy from May 2011 to January 2015

**Patient population**

Relapsed/refractory DLBCL

**Overall sample**

153

**Age (years), median (range)**

72 (25, 93)

75/153 (49.0)

**Male, n/N (%)**

Not specified.

**Baseline characteristics**

| ECOG performance status, n/N (%) | ISS disease stage, n/N (%) |
|----------------------------------|-----------------------------|
| 0–1                              | I/II                        |
| 2                                | III                         |
| 3                                | IV                          |

| Median number of prior treatment regimens (range) | Patients with GCB, n/N (%) |
|-------------------------------------------------|---------------------------|
| Not specified.                                  |                           |

**Maintenance therapy**

Oral lenalidomide (starting dose of 10, 15, 20, 25 mg/day) for 21 days of a 28-day cycle until disease progression or relapse; initial dosing and dose adjustments at the physician’s discretion

**Outcomes**

Response, safety, and outcome

*NHL, non-Hodgkin’s lymphoma; ECOG, Eastern Cooperative Oncology Group; DLBCL, diffuse large B-cell lymphoma; GCB germinal center B-cell-like; IPI, International Prognostic Index; ISS, International Staging System.

### TABLE 2 | Results from the risk of bias in non-randomized studies of interventions (ROBIN-I) tool.

| Author (year) | Confounding | Selection of participants | Classification of interventions | Deviations from intended interventions | Missing data | Measurement of outcomes | Selection of reported result | Risk of Bias score |
|---------------|-------------|----------------------------|---------------------------------|----------------------------------------|--------------|------------------------|-------------------------|-------------------|
| Wiernik et al. (6) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 4/7 |
| Hernandez-Illizaliturri et al. (14) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 4/7 |
| Witzig et al. (15) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 6/7 |
| Lakshmaiah et al. (16) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 4/7 |
| Zinzini et al. (17) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 4/7 |
| *Mondello et al. (18) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 5/7 |
| Czuczaman et al. (19) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 6/7 |
| Ferreri et al. 2017&2020 (20, 21) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 6/7 |
| Beylot-Barry et al. (7) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 6/7 |
| Broccoli et al. (22) | ![Confusion](https://example.com/confusion) | ![Participant Selection](https://example.com/participant) | ![Intervention Classification](https://example.com/classification) | ![Deviation from Intention](https://example.com/deviation) | ![Missing Data](https://example.com/missing) | ![Outcome Measurement](https://example.com/measurement) | ![Result Selection](https://example.com/result) | 4/7 |

*Low bias, High bias, Unclear bias.

*R randomised controlled trial that was only analyzed as a one-arm assessment observational study.
The results indicated that patients with non-GCB status had a greater ORR (0.50; 95% CI: 0.26, 0.74) than those with GCB status (0.06; 95% CI: 0.03, 0.11). The non-GCB group also had significantly better CR and PR (both $P < 0.05$).

The most serious treatment-related adverse events (AEs; Grade 3 or more) were neutropenia, thrombocytopenia, respiratory disorder, anemia, and diarrhea, and their mean cumulative incidences ranged from 2% to 28% (Table 3).

**Figure 3.** The results indicated that patients with non-GCB status had a greater ORR (0.50; 95% CI: 0.26, 0.74) than those with GCB status (0.06; 95% CI: 0.03, 0.11). The non-GCB group also had significantly better CR and PR (both $P < 0.05$).
Eight studies reported survival data. The median PFS ranged from 2.6 to 34 months and the median OS ranged from 7.8 to 37 months (Table 4). The study by Mondello et al. (18) reported distinctly better survival rates than the other studies. Further analysis indicated the Mondello et al. study examined patients who were less likely to be high-risk (34%), received fewer early treatment lines (mean: 1), and had longer median response times to the first treatment (median: 23 months).

### Publication Bias

Analysis of publication bias indicated no evidence of this bias based on a symmetric funnel plot and the results of the Egger’s test ($P = 0.778$; Figure 4).

### Survival Data

Our meta-analysis of 10 studies that examined the effect of lenalidomide monotherapy for DLBCL patients with R/R status indicated the ORR was 0.33 (95% CI: 0.26, 0.40). Moreover, patients with the non-GCB phenotype had a greater ORR (0.50; 95% CI: 0.26-0.74) than those with the GCB phenotype (0.06; 95% CI: 0.03, 0.11). The major serious treatment-related AEs in these patients were neutropenia, thrombocytopenia, respiratory disorder, anemia, and diarrhea. The median PFS ranged from 2.6 to 34 months and the median OS ranged from 7.8 to 37 months.

The introduction of lenalidomide treatment for DLBCL patients who have R/R status provides an opportunity for them to overcome chemorefractoriness (5). The anti-cancer effects of...
lenalidomide are due to its stimulation of cereblon, a component of E3 ubiquitin-ligase, and restoration of the function of immune effector cells (23). Our meta-analysis indicated the cumulative ORR (0.33; 95% CI 0.26, 0.40) was similar to that achieved by obinutuzumab monotherapy (0.32) (24) and tafasitamab monotherapy (ORR: 0.26–0.29) (25). Furthermore, trials have shown that combining lenalidomide and tafasitamab had higher efficacy than the single drug each, which indicated the synergistic
effect between the two drugs (26, 27). Because lenalidomide is an immunomodulatory agent, clinicians have used it for maintenance therapy and in various induction and salvage regimens (28). However, the evidence of a benefit of lenalidomide for DLBCL patients with R/R status is still limited. Some trials (e.g., NCT03730740) are now examining the efficiency of lenalidomide monotherapy as maintenance treatment for R/R non-Hodgkin T-cell lymphoma.

The GCB and non-GCB phenotypes of DLBCL have significant differences in prognosis (29, 30), and these phenotype have approximately the same prevalence among DLBCL patients (31). Although there are several moderating factors, patients with the non-GCB phenotype have better prognosis (32). In agreement, our meta-analysis indicated the non-GCB phenotype have approximately the same prevalence among DLBCL patients (31). Although there are several moderating factors, patients with the non-GCB phenotype have better prognosis (32). In agreement, our meta-analysis indicated the non-GCB phenotype have approximately the same prevalence among DLBCL patients (31). Although there are several moderating factors, patients with the non-GCB phenotype have better prognosis (32).

Previous studies reported the AEs of lenalidomide monotherapy were generally manageable (5). The most frequent serious AE in our 10 included studies was neutropenia (0.28; 95% CI: 0.20, 0.37). One study that compared placebo with lenalidomide reported a greater risk of neutropenia in the lenalidomide group (RR: 4.74; 95% CI: 2.96, 7.57) (35). Therefore, in routine clinical practice, prevention and appropriate management of neutropenia are important when administering lenalidomide monotherapy.

Because of the limited data in the available studies, we were unable to assess survival rates. However, Mondello et al. reported better survival rates than the other studies due to their methods of patient selection. In particular, they included fewer patients with high-risk (34%), patients who received fewer early treatment lines (mean: 1), and patients who had longer median response times for the first treatment (median: 23 months) (18). Further investigations are needed to confirm the effects of these different factors on survival of these patients.

To our best knowledge, the present systematic review is the first to examine the effect of lenalidomide monotherapy for DLBCL patients with R/R status. Our results indicated this treatment was active and tolerable, but these results should be considered with caution because the data were mostly from low-quality observational studies. For instance, one of the limitations of the present systematic review is the presence of selection bias regarding patient inclusion. Large and rigorously designed studies on this topic are needed to confirm the efficiency and safety of lenalidomide monotherapy for DLBCL patients with R/R status.

CONCLUSION

The results of the present study suggest that lenalidomide monotherapy was active for DLBCL patients with R/R status and leads to AEs that are mostly manageable. The non-GCB subgroup of these patients had greater tumor responsiveness than the GCB subgroup.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

OB designed and JL performed most of the investigation, data analysis and wrote the manuscript. JZ, WG, XW, and YZ provided data collection assistance. JZ contributed to interpretation of the data and analyses. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.756728/full#supplementary-material

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