

Maintenance therapy for untreated diffuse large B-cell lymphoma: a systematic review and network meta-analysis

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Abstract

Background: Several clinical trials have been conducted to evaluate the role of maintenance therapy in untreated diffuse large B-cell lymphoma (DLBCL) patients with complete response or partial response following standard immunochemotherapy; however, the effect of maintenance therapy remains uncertain, and a suitable maintenance strategy has not been determined because of the lack of direct/indirect comparisons.

Methods: We performed a systematic review and Bayesian network meta-analysis (NMA) to analyze and compare the effectiveness of different maintenance regimens in newly diagnosed DLBCL patients. We searched the *PubMed Medline, Embase, Web of Science, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials* for relevant papers from inception to 18 March 2021. Our study was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42020168864). Data on overall survival (OS) were extracted and the treatments were ranked using the surface under the cumulative ranking (SUCRA) curve.

Results: Eight trials and seven treatments involving 3525 patients were analyzed. OS analysis indicated that none of the drugs showed any benefit compared with non-maintenance therapy. Maintenance therapy with lenalidomide (SUCRA 69.3%) was ranked first in terms of OS.

Conclusion: Based on the OS results observed in this NMA, we do not recommend maintenance therapy in patients with newly diagnosed DLBCL after first-line therapy.

Keywords: chemotherapy, diffuse large B-cell lymphoma, maintenance therapy, meta-analysis, targeted therapy

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), accounting for 30–40% of all NHL cases.¹ DLBCL is a potentially curable disease; during the last two decades, the addition of rituximab (R) to standard chemotherapeutic drugs including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has improved the outcome of patients with DLBCL.^{2,3} R-CHOP has therefore emerged as the standard first-line immunochemotherapy for newly diagnosed DLBCL patients. However, >30% of DLBCL patients relapse within the first 2–3 years, leading to a poor prognosis.⁴

It has been shown that maintenance with rituximab is associated with improved outcomes in indolent NHL.⁵ To prevent relapse and improve the survival of DLBCL patients, clinical investigators have made considerable efforts regarding subsequent treatment after front-line therapy. Recently, increasing attention has been focused on maintenance therapy following induction therapy-induced remission.

Several clinical trials have been conducted with drugs, including rituximab, lenalidomide, enzastaurin, everolimus, and thalidomide among others, to evaluate the efficacy of maintenance therapy

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for untreated DLBCL patients with complete response (CR) or partial response (PR) after standard immunochemotherapy.⁶⁻¹³ Subgroup analyses of some clinical trials indicate that maintenance therapy has differences in gender⁷ and induction protocol,⁸ which suggests that it is a promising strategy for future research on the choice of drugs and potentially a highly selected group of patients.

However, the effect of maintenance therapy remains uncertain, and a suitable maintenance strategy has not been determined due to the lack of direct/indirect comparisons. It has been reported that rituximab maintenance improved survival in male patients with DLBCL after standard therapy.⁷ However, Habermann *et al.*⁸ reported that no benefit was provided by maintenance therapy after R-CHOP. It has been indicated that 2 years of lenalidomide maintenance in patients responding to R-CHOP significantly improved progression free survival, without a significant impact on overall survival (OS).¹¹ To determine the suitable maintenance strategies and estimate the ranking and hierarchy of them in DLBCL patients, we conducted a network meta-analysis (NMA), which can compare multiple interventions under the similar condition.

We first performed a systematic literature review of randomized controlled trials (RCTs) in newly diagnosed DLBCL cases to evaluate the maintenance treatments using different agents, and then conducted an NMA to compare the OS of each agent *versus* the others. This paper provides evidence that can enable the design of clinical trials for the maintenance treatment of DLBCL patients in the future.

Methods

Study design

This systematic review and NMA was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^{14,15} Our study was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42020168864)

Search strategy and selection criteria

We reviewed studies evaluating patients newly diagnosed with DLBCL and with response to standard immunochemotherapy including rituximab that

compare maintenance therapy with placebo/observation or compare different agents for maintenance with each other. We systematically searched *PubMed Medline*, *Embase*, *Web of Science*, *Cochrane Database of Systematic Reviews*, and *Cochrane Central Register of Controlled Trials* for relevant papers from inception to 18 March 2021. The search terms were “diffuse large B cell lymphoma” and “maintenance”. The language of the articles was restricted to English. We also conducted manual searches for the references of each study to ensure that no articles were missed.

The following eligibility criteria were considered: population, study design, interventions, comparisons, and outcomes. The inclusion criteria were as follows: (a) RCTs that evaluated the response of newly diagnosed DLBCL patients (adults) to standard immunochemotherapy; (b) parallel design RCTs fulfilling the criteria of population/problem, intervention, comparison, outcome, and study type;¹⁵ (c) prospective phase II or phase III RCTs that included rituximab in pre-maintenance therapy and compared at least two maintenance approaches; (d) RCTs that included the comparison of agents including placebo and no maintenance; and (e) RCTs that reported survival data including OS. We excluded studies in which patients did not receive rituximab as part of the induction therapy because this is no longer considered standard therapy.

Two investigators independently reviewed and selected studies according to the PRISMA diagram.¹⁶ All disagreements between the two reviewers (TY and XZ) were resolved by discussion with a third investigator (FZ, QY, or YL).

Data extraction

Two independent reviewers extracted the following information from all the eligible studies: name of the first author, year of publication, study phase, number of patients included in each arm, study enrollment period, months of median follow-up, pre-maintenance therapy, agents for maintenance of each arm, treatment schedule of every maintenance therapy, months of median duration of maintenance therapy, hazard ratios (HRs) and confidence intervals (CIs) for OS.

Whenever data were unavailable in the full-text studies, we estimated the HR using the ratio between the probabilities of the two arms and estimated the 95% CI using the *p* value.¹⁷

Quality assessment

We used the Cochrane risk of bias tool to evaluate the risk of bias of each RCT that was included.¹⁸ Two authors independently assessed the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

Statistical analysis

The primary outcome was the OS. We conducted the Bayesian NMA for OS in a random-effect model using the natural log transformations of HRs, and their 95% CIs, to estimate standard errors. No maintenance/placebo was selected as a common comparator to include all trials within one framework. The placebo treatment was assumed to be equivalent to no maintenance regarding the efficacy level. Our NMA does not involve direct or indirect pairwise comparisons; therefore, we conducted a Bayesian consistency framework.

The software used in our study was Stata software (version 15.1) and R-project statistical software (version 3.6.1) with the gemtc package and JAGS package. Bayesian NMA was performed in a random-effect model using Markov chain Monte Carlo methods. For our outcome measure, three Markov chains were simultaneously run in parallel for 80,000 interactions with 10,000 burn-ins per chain to obtain the posterior distribution. Treatment effects were estimated using HR and the corresponding 95% CI. We calculated the surfaces under the cumulative ranking curves (SUCRA) to rank the probabilities of all included treatments. SUCRA represents 1 if the treatment is certain to be ranked first and 0 if it is certain to be the last.^{19,20}

$$\text{SUCRA}_j = \frac{\sum_{b=1}^{a-1} \text{cum}_j, b}{a-1}$$

Results

Study selection and characteristics

We identified 754 articles from our original literature search. After duplicates were removed and the titles and abstracts were screened, 35 articles were considered for full-text assessment. Finally, eight articles involving 3525 patients met the eligibility criteria for NMA (Figure 1).

The main characteristics of the eight RCTs are listed in Table 1. Most of the enrolled trials were published within the last 5 years. There were five phase III trials and two phase II trials. The median follow-up period ranged from 32 to 81 months. Most of the pre-maintenance treatments included R-CHOP or R-CHOP-like regimens. Seven maintenance options were evaluated: enzastaurin, rituximab, lenalidomide, lenalidomide plus rituximab, everolimus, thalidomide, and observation/placebo. The main results of the eight RCTs are presented in Table 2.

The network established for NMA in our outcome is shown in Figure 2, where direct comparisons between drugs are represented by solid lines.

Risk of bias

The risk of bias in the included trials is shown in Figure 3. The overall quality of the included trials was adequate. Regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases, all the included RCTs were rated as “low risk”.

NMA

Compared with non-maintenance therapy through NMA, none of the drugs showed any benefit in improving OS, and the results showed no statistical difference (Figure 4).

Maintenance therapy with lenalidomide (SUCRA 69.3%) was ranked first in terms of OS; enzastaurin (SUCRA 58.8%) and thalidomide (SUCRA 57%) were ranked the second and third respectively (Figure 4) (Supplemental material Figure s1 online).

Discussion

Maintenance therapy is a strategy to maintain the initial response to induction therapy, prolong remission duration, delay relapse, and increase long-term survival by inhibiting cell proliferation. Maintenance therapy has been successfully used in a broad range of neoplasms, such as multiple myeloma or indolent lymphoma.²¹⁻²⁴ In the past decades, maintenance strategies have been used in clinical trials for DLBCL.⁶⁻¹³ However, the role of maintenance therapy in DLBCL remains uncertain, and there is a lack of clinical trials that directly

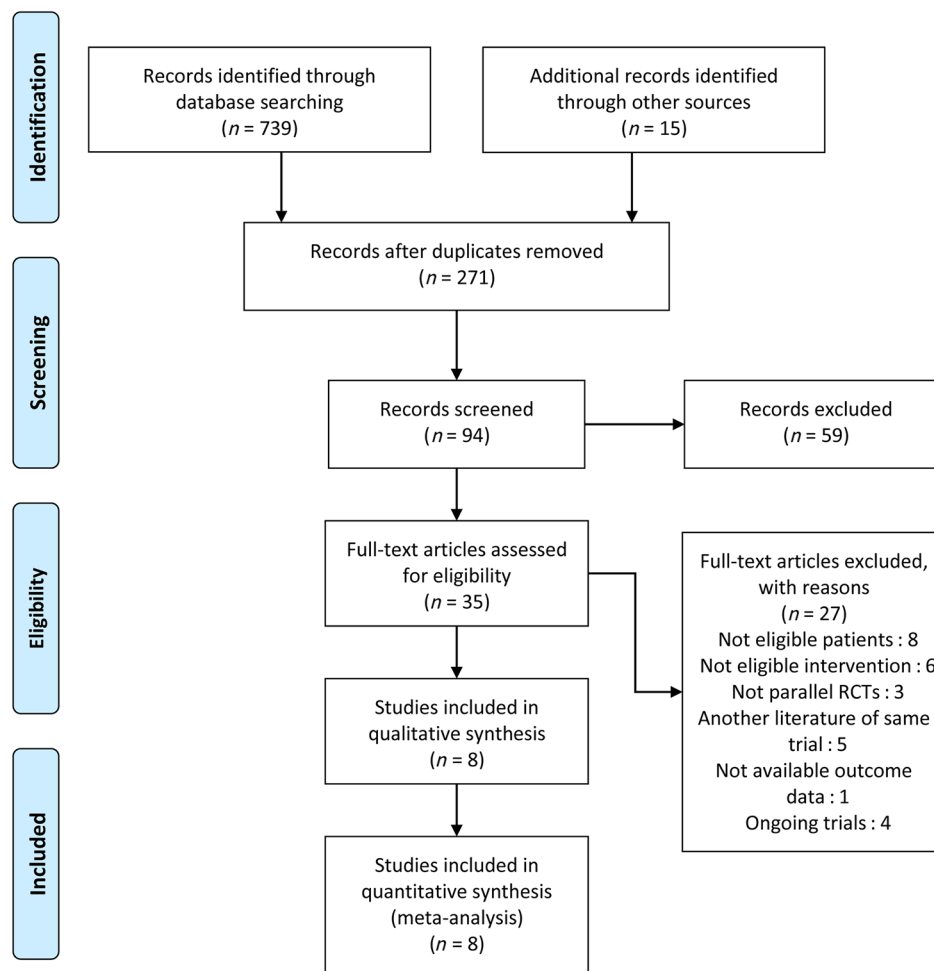


Figure 1. Literature search and selection. Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flow chart of the study selection for the network meta-analysis. RCT, randomized controlled trial.

compare the efficacy of different maintenance drugs.

We conducted the present systematic review and NMA using Bayesian statistics to compare the efficacy of drugs and drug combinations for maintenance therapy in newly diagnosed DLBCL patients after standard therapy. The OS was chosen as the primary outcome and results suggest that maintenance therapy provides no benefit.

To the best of our knowledge, this study is the first NMA to estimate the comparative efficacy of different drugs used in maintenance therapy after first-line immunotherapy for newly diagnosed DLBCL patients. A systematic literature review of PubMed revealed just one meta-analysis study that assessed

the role of maintenance therapy in patients with DLBCL who achieved CR or PR after first-line therapy.²⁵ Assessing OS as the primary outcome, our results, which showed that maintenance therapy did not affect the OS, were consistent with those of that study. There are several differences between the studies. First, in the meta-analysis by Rozental *et al.*, not all studies included rituximab in the induction therapy; the immunochemotherapy containing rituximab is currently standard therapy for DLBCL, therefore we excluded the studies in which patients did not receive rituximab as part of the induction therapy. Second, they conducted a traditional meta-analysis to compare maintenance and non-maintenance therapy; we conducted an NMA to compare multiple maintenance drugs. Third, they performed subgroup and adverse event

Table 1. Selected trials – trial characteristics.

ID	Trial	Phase	Number of patients included	Enrollment period	Median follow-up (months)	Pre-maintenance therapy	Experimental arm			Control arm		
							Treatment	Treatment schedule	Median duration of maintenance therapy (months)	Treatment	Treatment schedule	Median duration of maintenance therapy (months)
1	Crump <i>et al.</i> ⁶	III	758	NA	48	R-CHOP	Enzastaurin	500 mg/day	33.9	Placebo		34.7
2	Witzens-Harig <i>et al.</i> ⁷	III	152	2002–2011	32	Standard treatment	Rituximab	375 mg/m ² every 3 months	24	Observation		24
3	Habermann <i>et al.</i> ⁸	NA	415	1998–2001	42	R-CHOP	Rituximab	Four courses at 6-month intervals, with each course consisting of 375 mg/m ² weekly	24	Observation		24
4	Jaeger <i>et al.</i> ⁹	III	662	2004–2010	45	R-CHOP-like	Rituximab	375 mg/m ² every 2 months	24	Observation		24
5	Reddy <i>et al.</i> ¹⁰	II	44	2008–2013	43.68	R-CHOP	Lenalidomide	Lenalidomide 25 mg/day on days 1–21 of every 28-day cycle	12	Lenalidomide + rituximab	Lenalidomide 20 mg/day on days 1–21 of every 28-day cycle, rituximab 375 mg/m ² intravenously on day 8 of odd-numbered cycles (cycles 1, 3, 5, 7, 9, and 11)	12
6	Thieblemont <i>et al.</i> ¹¹	III	650	2009–2014	81	R-CHOP	Lenalidomide	Lenalidomide 25 mg/day on days 1–21 of every 28-day cycle	24	Placebo		24
7	Witzig <i>et al.</i> ¹²	III	742	2009–2013	50.4	R-chemo	Everolimus	10 mg/day	12	Placebo		12
8	Huang <i>et al.</i> ¹³	II	102	NA	34.2	R-CHOP	Everolimus	5 mg/day	12	Thalidomide	100–300 mg/day	24

chemo, chemotherapy; NA, not available; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 2. Selected trials – trial results.

ID	Trial	Arm		No. of patients		OS		
		Experimental	Control	Experimental	Control	HR	95% CI	p value
1	Crump <i>et al.</i> ⁶	Enzastaurin	Placebo	504	254	1.04	0.741–1.468	0.807
2	Witzens-Harig <i>et al.</i> ⁷	Rituximab	Observation	77	75	0.843	NA	0.65
3	Habermann <i>et al.</i> ⁸	Rituximab	Observation	207	208	1.28	0.65–2.53	0.48
4	Jaeger <i>et al.</i> ⁹	Rituximab	Observation	329	333	0.81	0.49–1.34	0.4145
5	Reddy <i>et al.</i> ¹⁰	Lenalidomide	Lenalidomide + rituximab	22	22	2.94	NA	0.4
6	Thieblemont <i>et al.</i> ¹¹	Lenalidomide	Placebo	323	327	1.17	0.9–1.6	0.29
7	Witzig <i>et al.</i> ¹²	Everolimus	Placebo	372	370	0.75	0.51–1.10	NA
8	Huang <i>et al.</i> ¹³	Everolimus	Thalidomide	50	52	0.711	0.169–2.998	NA

CI, confidence interval; HR, hazard ratio; NA, not available; OS, overall survival.

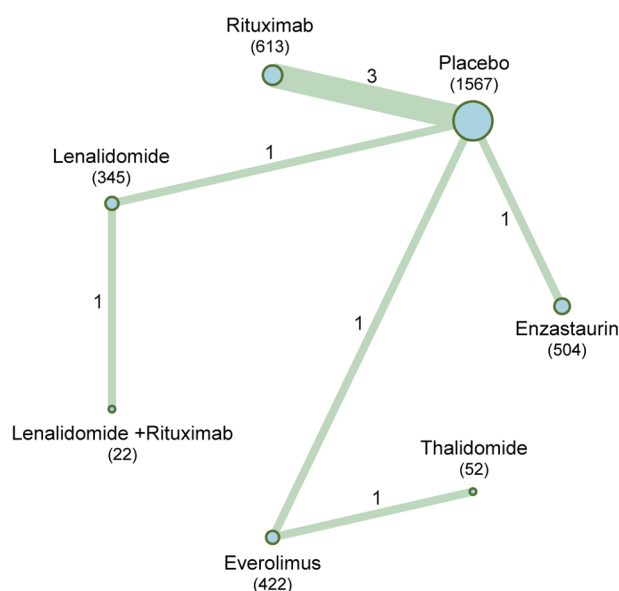


Figure 2. Network plot of all eligible trials assessing maintenance treatments for untreated diffuse large B-cell lymphoma. The size of each plot represents the number of patients (in brackets) receiving the corresponding intervention. The width of each line represents the number of trials (beside the line) of corresponding comparison.

analysis, which we were unable to perform due to the lack of relevant data in the included literature.

Traditional meta-analysis can only collect head-to-head RCTs of two treatments, for example, a certain drug and a placebo, and then draw a

conclusion about which one is preferred. NMA is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. There are six maintenance therapies in our study under the similar

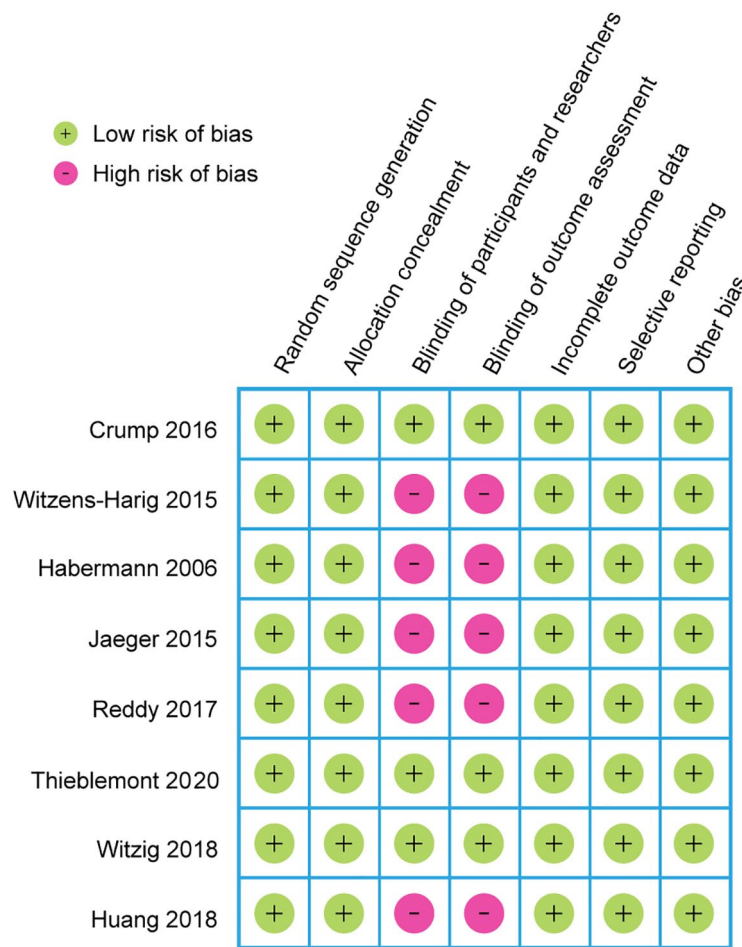


Figure 3. Assessment of the risk of bias in the included studies.
 +, low risk of bias; -, high risk of bias.

condition, therefore we use the Bayesian NMA as opposed to the classic meta-analysis. There are several advantages of NMA according to the Cochrane handbook. First, NMA can exploit all available direct and indirect evidence. Second, empirical studies have suggested it yields more precise estimates of the intervention effects in comparison with a single direct or indirect estimate. Third, NMA provides information for comparisons between pairs of interventions that have never been evaluated within individual randomized trials. In addition, the simultaneous comparison of all interventions of interest in the same analysis enables the estimation of their relative ranking for a given outcome.²⁶

Our study included eight RCTs, all of which reported OS as one of the outcomes. To synthesize

all the available evidence of maintenance therapy, we chose OS as the primary outcome. Generally, OS is the most important end point in clinical trials. DLBCL is an aggressive lymphoma that mostly relapses within the first 2–3 years; one study indicated that patients with DLBCL treated with standard immunochemotherapy who are event-free for 2 years have the same OS as the general population.²⁷ Event-free survival for 2 years is an appropriate criterion to evaluate agents for maintenance therapy in newly diagnosed DLBCL patients, which provides a reliable design scheme for future clinical trials and meta-analysis.

There are several points worthy of further study according to our comprehensive understanding of maintenance therapy in patients with newly diagnosed DLBCL.

Overall survival

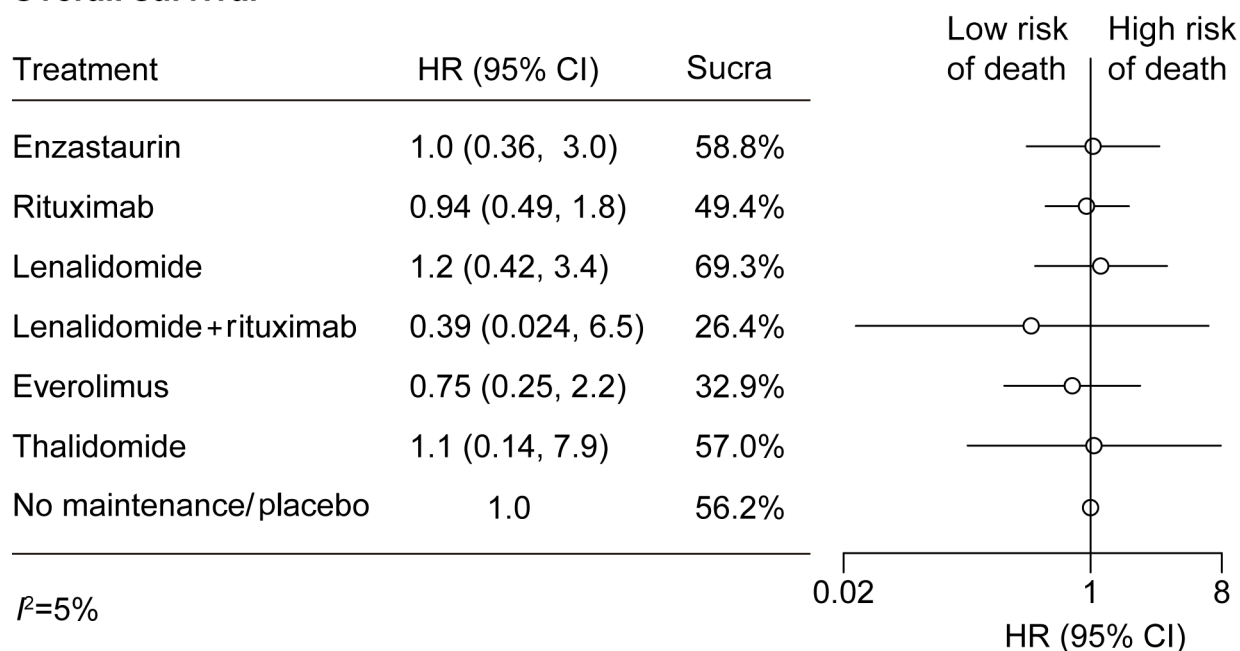


Figure 4. Forest plot of network meta-analysis results for overall survival. SUCRA represents the rank probabilities of all included treatments; it equals 1 if the treatment is certain to be ranked the first and 0 if it is certain to be the last. CI, confidence interval; HR, hazard ratio; SUCRA, surface under the cumulative ranking curve.

First, lenalidomide is an oral immunomodulatory agent with direct anti-tumor activity and immunologic effects. Its mechanism of action in neoplasms is yet to be fully determined. It has been used in several cancer types, such as multiple myeloma, myelodysplastic syndrome with 5q deletion, and relapsed/refractory mantle cell lymphoma.²⁸ Lenalidomide has significant single-agent activity in relapsed/refractory DLBCL.²⁹ Nowakowski *et al.*³⁰ reported that the combination of lenalidomide and R-CHOP therapy could overcome the negative prognostic impact of non-germinal center B-cell (non-GCB) phenotype on the outcome in newly diagnosed DLBCL patients. The current study evaluated the efficacy of lenalidomide as maintenance therapy for untreated DLBCL; the negative results could probably be attributed to the small sample size.

Second, rituximab has been applied as maintenance therapy in several types of lymphomas, such as follicular lymphoma and mantle cell lymphoma, with encouraging results.^{22,24,31,32} However, convincing evidence that maintenance with rituximab can improve the prognosis of patients with DLBCL after completion of first-line standard

treatment is still lacking. Three studies that evaluated the role of rituximab maintenance therapy in newly diagnosed DLBCL patients were included in our NMA. Two of them, through subgroup analysis, concluded that rituximab maintenance therapy improves outcomes in male DLBCL patients;^{7,9} men with a low international prognostic index (IPI) have better outcomes.⁹ However, small sample size and unplanned subgroup analysis limit the credibility of these results. This is an interesting question that needs to be addressed in future prospective trials.

Third, DLBCL is a heterogeneous disease, and the heterogeneity is derived from the clinical, pathological, and molecular biological aspects of recurrent somatic mutations in multiple genes that can affect cell regulation and proliferation. Heterogeneity leads to different therapeutic effects in patients with DLBCL. It has been reported that the prognosis is poor in DLBCL patients with the following characteristics: male, older age, more complications, higher tumor burden, higher level of lactate dehydrogenase, higher IPI score, non-GCB according to cell-of-origin (COO), higher Ki-67 proliferation index, P53

mutation, double/triple hits, and co-expression of *BCL6*, *BCL2*, and *MYC*.^{33–43} Individualized therapy according to patient characteristics is the focus of the current research. Therefore, it is necessary to conduct subgroup analysis, considering the different sources of heterogeneity in the design of clinical trials, which show exciting prospects for DLBCL maintenance therapy.

There are ongoing clinical trials that use other agents for DLBCL maintenance therapy after first-line immunochemotherapy. These drugs include bortezomib (phase III, NCT01965997), metformin (phase II, NCT03600363), and nivolumab (phase I, NCT03311958). We are awaiting exciting results from the ongoing DLBCL maintenance therapy clinical trials.

However, there are several limitations to our NMA. First, the results may be potentially affected by heterogeneity, which is caused by many factors, such as different inclusion criteria for the individual studies, inconsistent induction therapy, different protocols for a maintenance drug, and different follow-up durations. Second, very few RCTs were included in our study, and some comparisons included only one trial in our meta-analysis, such as lenalidomide *versus* placebo, lenalidomide *versus* lenalidomide plus rituximab, enzastaurin *versus* placebo, everolimus *versus* placebo, and everolimus *versus* thalidomide; therefore, the results may be considered as inconclusive evidence to some extent. More high-quality RCTs are essential to provide reliable proof. Third, our NMA did not conduct subgroup and adverse events analysis.

Conclusions

Our results do not support maintenance therapy in patients newly diagnosed with DLBCL, after first-line therapy. However, lenalidomide may be a potentially effective drug although the efficacy has to be confirmed by further clinical trials with more patients. The results of ongoing clinical trials which evaluate the effects of other agents such as bortezomib and metformin on maintenance therapy of newly diagnosed DLBCL patients are awaited. In addition, due to the heterogeneity of DLBCL, prospective subgroup design of clinical trials considering the sources of heterogeneity should be conducted in the future to identify the suitable drug for maintenance therapy in appropriate patients.

Author contributions

Conception and design, PC and XZ; development of methodology, TY and PC; acquisition of data, TY, YM, YL and FZ; formal analysis, TY and PC; writing, TY; reviewing and editing, PC and XZ. All authors contributed to the article and approved the submitted version.


Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997; 89: 3909–3918.
2. Coiffier B, Lepage E, Briere J, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346: 235–242.
3. Sehn LH, Donaldson J, Chhanabhai M, *et al.* Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol* 2005; 23: 5027–5033.
4. Karlin L and Coiffier B. Improving survival and preventing recurrence of diffuse large B-cell lymphoma in younger patients: current strategies and future directions. *Onco Targets Ther* 2013; 6: 289–296.

5. Tilly H, Gomes da Silva M, Vitolo U, *et al.* Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26(Suppl. 5): v116–v125.
6. Crump M, Leppä S, Fayad L, *et al.* Randomized, double-blind, phase III trial of enzastaurin versus placebo in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. *J Clin Oncol* 2016; 34: 2484–2492.
7. Witzens-Harig M, Benner A, McClanahan F, *et al.* Rituximab maintenance improves survival in male patients with diffuse large B-cell lymphoma. Results of the HD2002 prospective multicentre randomized phase III trial. *Br J Haematol* 2015; 171: 710–719.
8. Habermann TM, Weller EA, Morrison VA, *et al.* Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006; 24: 3121–3127.
9. Jaeger U, Trnecny M, Melzer H, *et al.* Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. *Haematologica* 2015; 100: 955–963.
10. Reddy NM, Greer JP, Morgan DS, *et al.* A phase II randomized study of lenalidomide or lenalidomide and rituximab as maintenance therapy following standard chemotherapy for patients with high/high-intermediate risk diffuse large B-cell lymphoma. *Leukemia* 2017; 31: 241–244.
11. Thieblemont C, Gomes Da Silva M, Casasnovas O, *et al.* Final analysis of the international double-blind randomized phase III study of lenalidomide maintenance in elderly patients with DLBCL in response after R-CHOP, the Remarc study from Lysa. *Blood* 2020; 136(Suppl. 1): 1–2.
12. Witzig TE, Tobinai K, Rigacci L, *et al.* Adjuvant everolimus in high-risk diffuse large B-cell lymphoma: final results from the PILLAR-2 randomized phase III trial. *Ann Oncol* 2018; 29: 707–714.
13. Huang H, Li XY, Hong HM, *et al.* Randomized, open-label, phase II trial of everolimus versus thalidomide in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. *J Clin Oncol* 2018; 36(Suppl. 15): 7560.
14. Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.
15. Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162: 777–784.
16. Moher D, Liberati A, Tetzlaff J, *et al.*; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
17. Altman DG and Bland JM. How to obtain the P value from a confidence interval. *BMJ* 2011; 343: d2304.
18. Higgins JP, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
19. Chaimani A, Higgins JP, Mavridis D, *et al.* Graphical tools for network meta-analysis in STATA. *PLoS One* 2013; 8: e76654.
20. Shim SR, Kim SJ, Lee J, *et al.* Network meta-analysis: application and practice using R software. *Epidemiol Health* 2019; 41: e2019013.
21. Wang Y, Yang F, Shen Y, *et al.* Maintenance therapy with immunomodulatory drugs in multiple myeloma: a meta-analysis and systematic review. *J Natl Cancer Inst* 2015; 108: djv342.
22. Salles G, Seymour JF, Offner F, *et al.* Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 2011; 377: 42–51.
23. Le Gouill S, Thieblemont C, Oberic L, *et al.* Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med* 2017; 377: 1250–1260.
24. Kluin-Nelemans HC, Hoster E, Hermine O, *et al.* Treatment of older patients with mantle-cell lymphoma. *N Engl J Med* 2012; 367: 520–531.
25. Rozental A, Gafter-Gvili A, Vidal L, *et al.* The role of maintenance therapy in patients with diffuse large B cell lymphoma: a systematic review and meta-analysis. *Hematol Oncol* 2019; 37: 27–34.
26. Chaimani A, Caldwell DM, Li T, *et al.* Chapter 11: Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, *et al.* (eds) *Cochrane handbook for systematic reviews of interventions*, version 6.2. Cochrane, 2021,

- www.training.cochrane.org/handbook (accessed 24 March 2021).
27. Maurer MJ, Ghesquières H, Jais JP, *et al.* Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol* 2014; 32: 1066–1073.
 28. Shah SR and Tran TM. Lenalidomide in myelodysplastic syndrome and multiple myeloma. *Drugs* 2007; 67: 1869–1881.
 29. Wiernik PH, Lossos IS, Tuscano JM, *et al.* Lenalidomide monotherapy in relapsed or refractory aggressive large B-Hodgkin's lymphoma. *J Clin Oncol* 2008; 26: 4952–4957.
 30. Nowakowski GS, LaPlant B, Macon WR, *et al.* Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. *J Clin Oncol* 2015; 33: 251–257.
 31. van Oers MH, Klasa R, Marcus RE, *et al.* Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. *Blood* 2006; 108: 3295–3301.
 32. Dietrich S, Weidle J, Rieger M, *et al.* Rituximab maintenance therapy after autologous stem cell transplantation prolongs progression-free survival in patients with mantle cell lymphoma. *Leukemia* 2014; 28: 708–709.
 33. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; 329: 987–994.
 34. Sehn LH, Berry B, Chhanabhai M, *et al.* The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007; 109: 1857–1861.
 35. Broyde A, Boycov O, Strenov Y, *et al.* Role and prognostic significance of the Ki-67 index in non-Hodgkin's lymphoma. *Am J Hematol* 2009; 84: 338–343.
 36. Salles G, de Jong D, Xie W, *et al.* Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. *Blood* 2011; 117: 7070–7078.
 37. Akyurek N, Uner A, Benekli M, *et al.* Prognostic significance of MYC, BCL2, and BCL6 rearrangements in patients with diffuse large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab. *Cancer* 2012; 118: 4173–4183.
 38. Hu S, Xu-Monette ZY, Tzankov A, *et al.* MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from the International DLBCL Rituximab-CHOP Consortium Program. *Blood* 2013; 121: 4021–4031; quiz 4250.
 39. Visco C, Tzankov A, Xu-Monette ZY, *et al.* Patients with diffuse large B-cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC status: a report from an International DLBCL Rituximab-CHOP Consortium Program Study. *Haematologica* 2013; 98: 255–263.
 40. Ye Q, Xu-Monette ZY, Tzankov A, *et al.* Prognostic impact of concurrent MYC and BCL6 rearrangements and expression in de novo diffuse large B-cell lymphoma. *Oncotarget* 2016; 7: 2401–2416.
 41. Lenz G, Wright G, Dave SS, *et al.* Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med* 2008; 359: 2313–2323.
 42. Alizadeh AA, Eisen MB, Davis RE, *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; 403: 503–511.
 43. Rosenwald A, Wright G, Chan WC, *et al.* The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346: 1937–1947.