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ORIGINAL RESEARCH

Rituximab-based combination therapy in patients with Waldenström macroglobulinemia: a systematic review and meta-analysis

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Background: To evaluate the efficacy and safety of rituximab-based combination therapy for Waldenström macroglobulinemia (WM), we conducted this meta-analysis by pooling the rates of overall response, major response, complete response, and grade ≥3 hematological adverse events.

Methods and materials: We searched for relevant studies in the databases of PubMed, Web of Science, Embase, and the Cochrane Library. The qualitative assessment of all the included articles was conducted with reference to the Newcastle–Ottawa Scale. A random-effects model was selected to perform all pooled analyses.

Results: We identified altogether 22 studies with a total of 806 symptomatic WM patients enrolled. The pooled analysis indicated that the rituximab-based combination therapy achieved an overall response rate (ORR) of 84% (95% CI: 81%–87%), a major response rate (MRR) of 71% (95% CI: 66%–75%), and a complete response rate (CRR) of 7% (95% CI: 5%–10%). Rituximab plus conventional alkylating agents–containing chemotherapy (subgroup A) yielded an ORR of 86% (95% CI: 81%–89%), an MRR of 74% (95% CI: 69%–79%), and a CRR of 8% (95% CI: 4%–14%). Rituximab plus purine analog (subgroup B) resulted in an ORR of 85% (95% CI: 79%–89%), an MRR of 74% (95% CI: 66%–81%), and a CRR of 9% (95% CI: 4%–15%). Rituximab plus proteasome inhibitor (subgroup C) resulted in an ORR of 86% (95% CI: 81%–90%), an MRR of 68% (95% CI: 58%–77%), and a CRR of 7% (95% CI: 3%–11%). Rituximab plus immunomodulatory drug (subgroup D) attained relatively lower response rates, with an ORR of 67% (95% CI: 51%–81%), an MRR of 56% (95% CI: 27%–83%), and a CRR of 5% (95% CI: 1%–12%). Common grade ≥3 hematological adverse events consisted of neutropenia (33%, 95% CI: 17%–52%), thrombocytopenia (7%, 95% CI: 3%–11%), and anemia (5%, 95% CI: 3%–9%).

Conclusion: Rituximab in combination with an alkylating agent, purine analog, or proteasome inhibitor is highly effective with tolerable hematological toxicities for WM.

Keywords: response rate, individualized therapy

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Introduction

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma (LPL) characterized by the infiltration of small B lymphocytes, lymphocytes with plasmacytoid differentiation, and plasma cells into the bone marrow and other lymphatic organs, along with a detectable serum monoclonal IgM.[1,2] WM is a rare B-cell chronic lymphoproliferative disorder with a median survival of 5–10 years, representing ~2% of all hematological malignancies. It is more common in men and Caucasians with a median age of >60–70 years.[3] Indolent as it is, WM remains an incurable disease.[4,5] Effective

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treatment is required for patients with symptomatic manifestations, which primarily consist of hyperviscosity, peripheral neuropathy, lymphadenopathy, hepatomegaly, splenomegaly, cytopenias, hemolytic anemia, and cryoglobulinemia.[6] A recurrent somatic mutation of the *MYD88* gene (*MYD88* Leu265Pro) has been detected in ~90% of patients with WM, which contributes to the differentiation of WM from other B-cell lymphoproliferative disorders.[7] *CXCR4* gene somatic mutations are also found in ~40% of patients. The mutation status of *MYD88* and *CXCR4* genes is indicative of response to a treatment, which can serve as predictive biomarkers in personalized therapeutics.[8]

Rituximab is a human–mouse chimeric monoclonal antibody targeting CD20 antigen, which is ubiquitously expressed on the surface of B cells. Rituximab adheres to CD20, leading to B-cell lysis mainly through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[9] When used as a single agent, rituximab has modest anti-WM potency and increases the risk of "IgM flare" phenomenon in which most patients suffer from an obvious elevation in the serum IgM level that aggravates hyperviscosity-related complications including fatigue, blurred vision, vertigo, epistaxis, headaches, and tachypnea. Urgent plasmapheresis is required.[10] In comparison with rituximab monotherapy,

"IgM flare" phenomenon is observed much infrequently when cytoreductive therapy with other anti-WM agents is administered before the infusion of rituximab.[11] Therefore, monotherapy is unsuitable, especially for patients with a high serum IgM level or a heavy tumor burden. Rituximab is the backbone of the treatment when used in combination with other agents such as proteasome inhibitors, immunomodulatory drugs, or conventional chemotherapeutic agents. However, in terms of response rate, the comparative outcomes among different combinations remain unknown. In addition, many clinical trials or retrospective studies enrolled only a small amount of patients due to the rarity of WM. We conducted this meta-analysis by pooling the response rates and hematological adverse events of different rituximab-based combinations in an attempt to provide a more comprehensive appraisal of the efficacy and safety for clinical practice.

Methods and materials

The reporting of this pooled analysis adhered to the PRISMA guidelines (Table 1).[12] Two investigators independently searched the databases, evaluated all potential articles, and extracted the required data (baseline characteristics and treatment outcomes) from the included articles. When confronted with discrepancies, they reached a consensus by discussion

Table 1 PRISMA checklist

Section/topic	Number	Checklist item	Reported on page number
Title			
Title	1	Identify the report as a systematic review, a meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3–4
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS.	3–4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	No registration
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4–5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4–5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4–5

(*Continued*)

Table 1 (*Continued*)

Section/topic	Number	Checklist item	Reported on page number
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5–6
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	5–6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	5–6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5–6
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	5–6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6–7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	6–7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7–8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group and 2) effect estimates and CIs, ideally with a forest plot.	7–8, Table 2, Figures 2–6
Synthesis of results	21	Present results of each meta-analysis done, including CIs and measures of consistency.	7–8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	8–9, Table 3
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	7–8
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy-makers).	9–11
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	12–13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	13
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	14

Notes: Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.1371/ journal.pmed1000097.[65]
Abbreviation: PICOS, participants, interventions, comparisons, outcomes, and study design.

or consulting a third senior investigator, who supervised all the research procedures.

Literature retrieval strategy and study selection criteria

We searched for relevant studies in the databases of PubMed, Web of Science, Embase, and the Cochrane Library, with language restricted to English. The following medical subject headings terms or keywords were used in the literature retrieval: "rituximab," "Rituxan," "anti-CD20," "Waldenström macroglobulinemia," "lymphoplasmacytic lymphoma," "lymphoplasmacytic neoplasm," and "B cell chronic lymphoproliferative diseases." By screening the references of all the retrieved articles, we also manually identified other potentially relevant studies to supplement our search. Multiple retrieved publications of the same study were considered as

one article, and only the most recent or the most informative one was included in this meta-analysis. The latest literature search was updated on May 31, 2018.

To warrant the authenticity of this pooled analysis, all the eligible studies had to meet all the following inclusion criteria: (1) The patients were diagnosed with symptomatic WM, including relapsed or refractory, previously untreated patients; (2) the therapeutic regimen must contain rituximab; (3) treatment outcomes were presented as response rates, whether the study be a retrospective study or a prospective clinical trial; and (4) the potentially included studies must provide sufficient information about the accurate number of patients who achieved any grade response status to treatment.

Articles falling into the following categories were excluded: (1) duplicated records, experimental and basic research, clinical guidelines, reviews, commentary, case reports, conference abstracts, and studies which provided inadequate information; (2) studies in which rituximab monotherapy was the treatment schedule; (3) studies that failed to differentiate WM from LPL; and (4) studies in which the response rate to treatment was assessed according to IgM level, not by means of serum protein electrophoresis (M-spike measurement), but using other approaches, such as nephelometry.

Qualitative assessment of articles and data extraction

The qualitative assessment of all the included articles was conducted with reference to the Newcastle–Ottawa Scale (NOS) for a single-arm nonrandomized trial, a randomized controlled trial (RCT), a cohort study, or a retrospective study (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

The primary objective of this pooled analysis was to determine the overall response rate (ORR), which included the rate of complete response (CR: immunofixation negativity in the serum monoclonal IgM), very good partial response (VGPR: ≥90% reduction in serum IgM levels), partial response (PR: ≥50% reduction), and minor response (≥25% reduction).[11,13] The secondary efficacy endpoints were complete response rate (CRR) and major response rate (MRR), which was defined as the sum of CR, VGPR, and PR. In terms of the safety outcome, we only discussed grade ≥3 hematological toxicity (anemia, neutropenia, and thrombocytopenia) on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. Therefore, we recorded the exact number of patients who achieved CR, VGPR, PR, and minor response

and suffered from grade ≥3 hematological adverse events in the predesigned table.

Statistical analysis

A random-effects model, which could provide more conservative results of treatment outcomes, was selected to perform all the pooled calculations, including ORR, MRR, CRR, and the rate of grade ≥3 hematological adverse events. The heterogeneity among studies was evaluated by means of Cochrane Q-test and was quantified using the I^2 statistics. We also conducted a subgroup analysis to explore the source of heterogeneity when necessary.

Considering the rarity of WM, we estimated that many potentially included studies had a small sample size. In order to avoid the bias caused by events with very low or even zero incidence rate and the possible small sample size of some included studies, the extracted data were empirically converted into double arcsine form after Freeman–Tukey double arcsine transformation. The transformed data were then used in pooled calculations with the random-effects model. Eventually, the pooled results were transformed back to their original form and were reported.

The comparison of categorical variables between two groups was done using Pearson's chi-squared test or Fisher's exact test. Comparisons between multiple different subgroups were performed with partitions of Pearson's chi-squared test by which a two-tailed P-value of less than adjusted α was considered statistically significant.

Publication bias for each synthesized calculation was evaluated using Egger's test and Begg's test, with $P < 0.05$ representing that there existed a significant publication bias. All meta-analysis and publication bias tests were performed with Stata statistical software Version 12.0 (Stata Corporation, College Station, TX, USA). All the tests were two-sided with $P < 0.05$ representing the statistical significance.

Results
Study search and characteristics

Figure 1 demonstrates the process by which studies were identified and selected for inclusion in our meta-analysis. We identified 362 potentially relevant articles through our initial database search. After screening the titles and abstracts, 327 articles were excluded. Among the remaining 35 articles, 13 articles were eliminated after full-text reading because they failed to provide sufficient outcome data or they did not differentiate WM from LPL. Ultimately, our meta-analysis included altogether 22 studies with a total of 806 symptomatic WM patients enrolled, among which 15 articles were
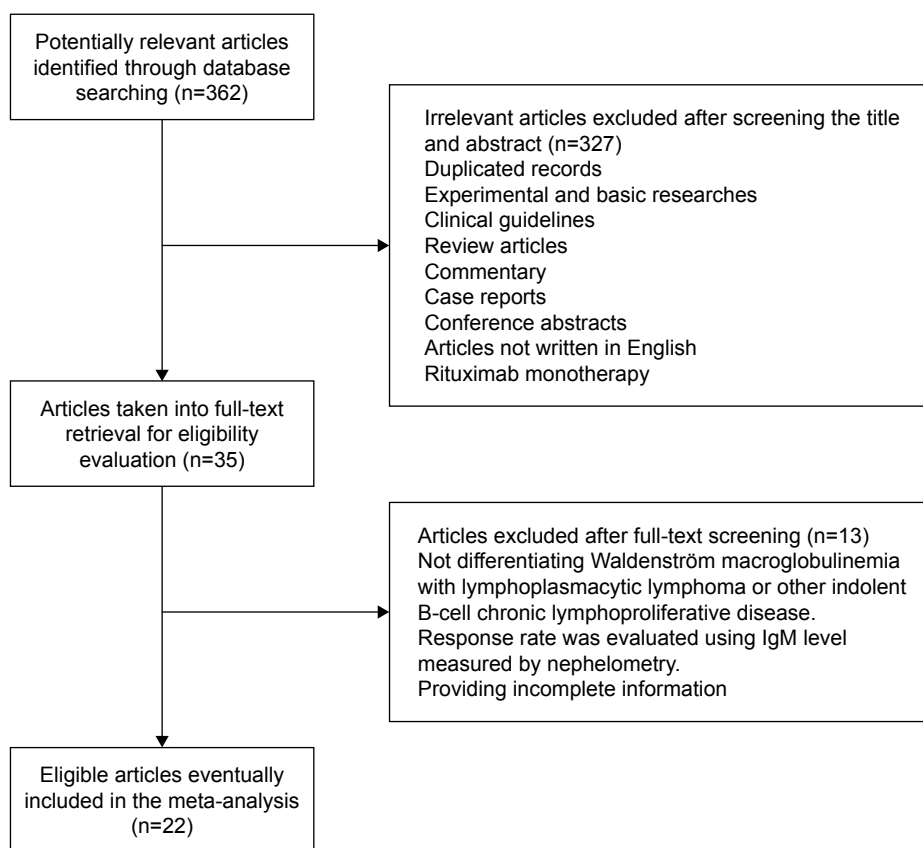
Figure 1 Selection of studies. Flow diagram demonstrating the identification and selection process of articles included in the meta-analysis.

single-arm phase II clinical trials, six articles were retrospective studies, and one article was a phase III RCT.[14–35] Six of the identified studies focused on previously untreated WM patients, five of the studies enrolled pretreated patients with relapsed or refractory WM, while the rest 11 studies enrolled both. It should be noted that one included study enrolled WM patients receiving three different therapeutic regimens, and then, we considered each treatment group as an independent study to conduct the pooled analysis.[19]

The NOS consists of eight items, which are classified into three main factors including patient selection (four items, one star awarded for each item), comparability of the study group (one item, two stars awarded for this item), and the assessment of outcome and follow-up (three items, one star awarded for each item). The NOS score ranges from zero to nine stars, with six or more stars considered to be of high quality. With respect to the sole RCT, we merely evaluated the experimental group (rituximab-based group) with reference to the NOS. All the studies in our meta-analysis obtained at least seven stars, indicating that the quality of the included original studies was fully guaranteed. Table 2 summarizes the study characteristics.

ORR, MRR, and CRR

To explore the source of heterogeneity, we further divided the included studies into four broad subgroups according to different therapeutic regimens. Conventional alkylating agents–containing chemotherapy group includes the cyclophosphamide + doxorubicin + vincristine + prednisone regimen, cyclophosphamide + vincristine + prednisone regimen, cyclophosphamide + dexamethasone regimen, cyclophosphamide + prednisone regimen, and bendamustine. Regimens that contain fludarabine or cladribine are categorized into purine analog group. Regimens that contain bortezomib or carfilzomib are classified into proteasome inhibitor group. Regimens that contain thalidomide or lenalidomide fall into immunomodulatory drug group.

As previously described, the extracted data were transformed into double arcsine form to be synthesized, and Figures 2–4 demonstrate the pooled rates. Then, the pooled rates of overall response, major response, and CR were transformed back to their original form as demonstrated in Figure 5.

The pooled analysis indicated that rituximab-based combination therapy achieved an ORR of 84% (95%
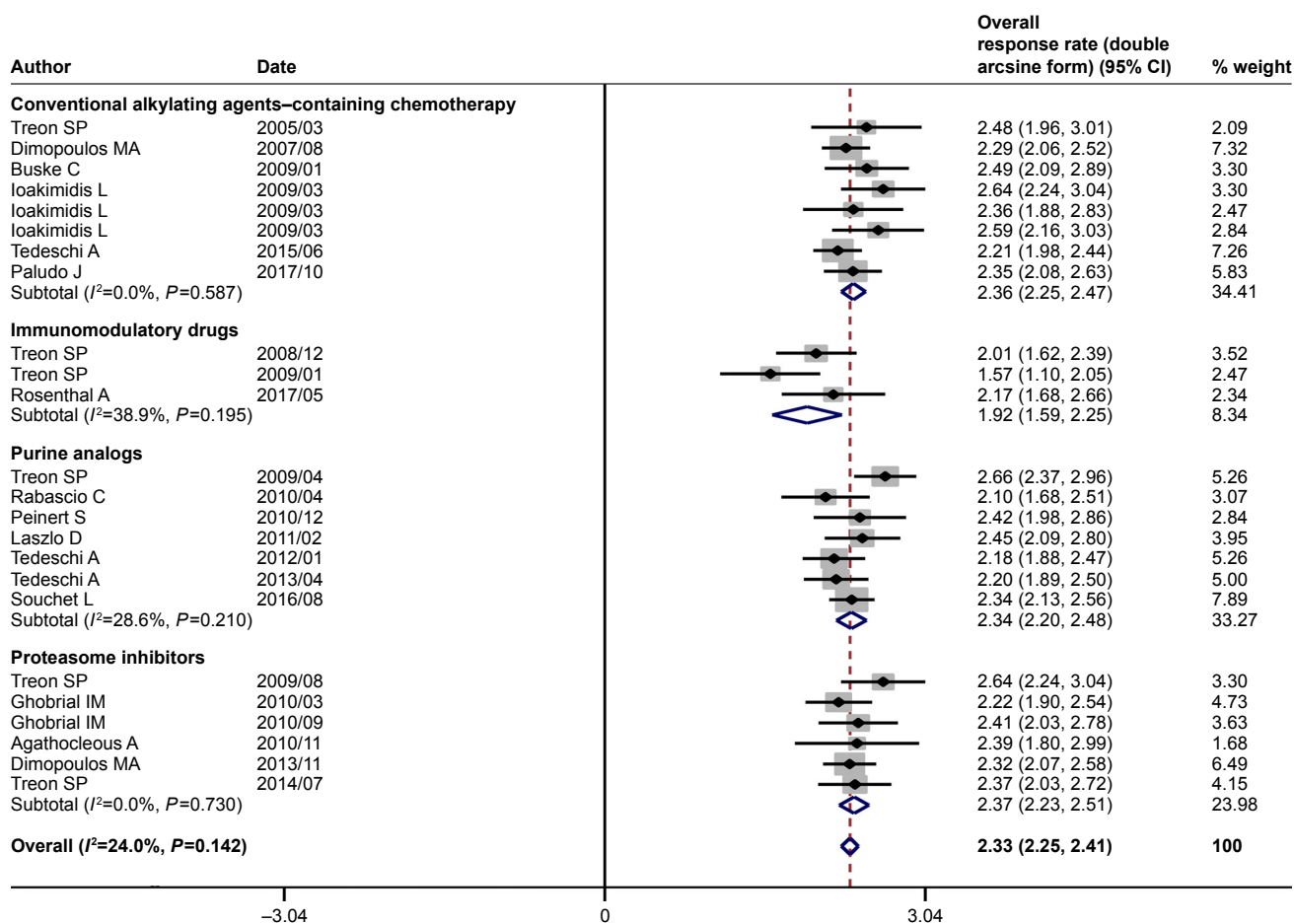
Table 2 Patient characteristics and treatment outcomes of the included studies

References	Study design	Total patients	Previous treatment	Median age (years)	Gender (male/ female)
Treon et al (2005/03)[14]	Clinical trial, Phase II; single-arm	13	Both (three previously untreated)	54	NA
Dimopoulos et al (2007/08)[15]	Clinical trial, Phase II; single-arm	72	Previously untreated	69	45/27
Treon et al (2008/12)[16]	Clinical trial, Phase II; single-arm	25	Both (20 previously untreated)	62	NA
Buske et al (2009/01)[17]	Clinical trial, Phase III; RCT	23	Previously untreated	58	15/8
Treon et al (2009/01)[18]	Clinical trial, Phase II; single-arm	16	Both (12 previously untreated)	65	12/4
Ioakimidis et al (2009/03)[19]	Retrospective study	23	Both (13 previously untreated)	54	NA
		16	Both (five previously untreated)	60	NA
		19	Both (12 previously untreated)	65	NA
Treon et al (2009/04)[20]	Clinical trial, Phase II; single-arm	43	Both (27 previously untreated)	61	NA
Treon et al (2009/08)[21]	Clinical trial, Phase II; single-arm	23	Previously untreated	66	NA
Ghobrial et al (2010/03)[22]	Clinical trial, Phase II; single-arm	37	Relapsed or refractory	64	26/11
Rabascio et al (2010/04)[23]	Retrospective study	21	Both	NA	NA
Ghobrial et al (2010/09)[24]	Clinical trial, Phase II; single-arm	26	Previously untreated	62.5	15/11
Agathocleous et al (2010/11)[25]	Clinical trial, Phase II; single-arm	10	Relapsed or refractory	NA	NA
Peinert et al (2010/12)[26]	Retrospective study	19	Both	NA	NA
Laszlo et al (2011/02)[27]	Clinical trial, Phase II; single-arm	29	Both (16 previously untreated)	64	19/10
Tedeschi et al (2012/01)[28]	Clinical trial, Phase II; single-arm	43	Both	65	25/18
Tedeschi et al (2013/04)[29]	Retrospective study	40	Relapsed or refractory	67	28/12
Dimopoulos et al (2013/11)[30]	Clinical trial, Phase II; single-arm	59	Previously untreated	70	38/21
Treon et al (2014/07)[31]	Clinical trial, Phase II; single-arm	31	Both (28 previously untreated)	61	19/12
Tedeschi et al (2015/06)[32]	Retrospective study	71	Relapsed or refractory	72	46/25
Souchet et al (2016/08)[33]	Retrospective study	82	Both (25 previously untreated)	NA	NA
Rosenthal et al (2017/05)[34]	Clinical trial, Phase II; single-arm	15	Previously untreated	NA	NA
Paludo et al (2017/10)[35]	Clinical trial, Phase II; single-arm	50	Relapsed or refractory	68	NA

Notes: The references of the included studies were presented in chronological order according to their published date. The term "both" indicates that the study enrolled both patients who had previous therapy and previously untreated patients.
Abbreviations: CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; CR, complete response; NA, not available; PR, partial response; RCT, randomized controlled trial; VGPR, very good partial response.

Treatment regimen	CR	VGPR	PR	Minor response	Major response	Overall response	Anemia (grade ≥3)	Neutropenia (grade ≥3)	Thrombocytopenia (grade ≥3)
Rituximab + CHOP	3	NA	8	I	11	12	NA	NA	NA
Rituximab + cyclophosphamide + dexamethasone	5	NA	48	7	53	60	NA	9	0
Rituximab + thalidomide	I	NA	15	2	16	18	NA	NA	NA
Rituximab + CHOP	2	NA	19	NA	21	21	NA	NA	NA
Rituximab + lenalidomide	0	NA	NA	4	4	8	I	5	I
Rituximab + CHOP	4	2	10	6	16	22	NA	NA	NA
Rituximab + cyclophosphamide + vincristine + prednisone	2	I	7	4	10	14	NA	NA	NA
Rituximab + cyclophosphamide + prednisone	0	0	14	4	14	18	NA	NA	NA
Rituximab + fludarabine	2	14	21	4	37	41	I	27	7
Rituximab + bortezomib + dexamethasone	5	3	11	3	19	22	I	7	2
Rituximab + bortezomib	2	NA	17	11	19	30	4	6	5
Rituximab + cladribine (2-CdA)	I	NA	10	5	11	16	NA	NA	NA
Rituximab + bortezomib	I	I	15	6	17	23	2	3	2
Rituximab + bortezomib	0	NA	9	NA	9	9	NA	NA	NA
Rituximab + fludarabine ± cyclophosphamide	I	NA	14	2	15	17	NA	NA	NA
Rituximab + cladribine (2-CdA)	7	NA	16	3	23	26	NA	NA	NA
Rituximab + fludarabine + cyclophosphamide	5	9	18	2	32	34	I	38	2
Rituximab + fludarabine + cyclophosphamide	4	9	19	0	32	32	NA	35	NA
Rituximab + bortezomib + dexamethasone	2	4	34	10	40	50	0	9	3
Rituximab + carfilzomib + dexamethasone	I	10	10	6	21	27	I	3	0
Rituximab + bendamustine	5	11	37	4	53	57	NA	4	2
Rituximab + fludarabine + cyclophosphamide	I	14	38	17	53	70	7	35	11
Rituximab + lenalidomide + cyclophosphamide + dexamethasone	I	NA	11	NA	12	12	NA	NA	NA
Rituximab + cyclophosphamide + dexamethasone	0	2	32	9	34	43	NA	NA	NA

Author	Date		Overall response rate (double arcsine form) (95% CI)	% weight
Conventional alkylating agents–containing chemotherapy				
Treon SP	2005/03		2.48 (1.96, 3.01)	2.09
Dimopoulos MA	2007/08		2.29 (2.06, 2.52)	7.32
Buske C	2009/01		2.49 (2.09, 2.89)	3.30
Ioakimidis L	2009/03		2.64 (2.24, 3.04)	3.30
Ioakimidis L	2009/03		2.36 (1.88, 2.83)	2.47
Ioakimidis L	2009/03		2.59 (2.16, 3.03)	2.84
Tedeschi A	2015/06		2.21 (1.98, 2.44)	7.26
Paludo J	2017/10		2.35 (2.08, 2.63)	5.83
Subtotal (I^2=0.0%, P=0.587)			2.36 (2.25, 2.47)	34.41
Immunomodulatory drugs				
Treon SP	2008/12		2.01 (1.62, 2.39)	3.52
Treon SP	2009/01		1.57 (1.10, 2.05)	2.47
Rosenthal A	2017/05		2.17 (1.68, 2.66)	2.34
Subtotal (I^2=38.9%, P=0.195)			1.92 (1.59, 2.25)	8.34
Purine analogs				
Treon SP	2009/04		2.66 (2.37, 2.96)	5.26
Rabascio C	2010/04		2.10 (1.68, 2.51)	3.07
Peinert S	2010/12		2.42 (1.98, 2.86)	2.84
Laszlo D	2011/02		2.45 (2.09, 2.80)	3.95
Tedeschi A	2012/01		2.18 (1.88, 2.47)	5.26
Tedeschi A	2013/04		2.20 (1.89, 2.50)	5.00
Souchet L	2016/08		2.34 (2.13, 2.56)	7.89
Subtotal (I^2=28.6%, P=0.210)			2.34 (2.20, 2.48)	33.27
Proteasome inhibitors				
Treon SP	2009/08		2.64 (2.24, 3.04)	3.30
Ghobrial IM	2010/03		2.22 (1.90, 2.54)	4.73
Ghobrial IM	2010/09		2.41 (2.03, 2.78)	3.63
Agathocleous A	2010/11		2.39 (1.80, 2.99)	1.68
Dimopoulos MA	2013/11		2.32 (2.07, 2.58)	6.49
Treon SP	2014/07		2.37 (2.03, 2.72)	4.15
Subtotal (I^2=0.0%, P=0.730)			2.37 (2.23, 2.51)	23.98
Overall (I^2=24.0%, P=0.142)			**2.33 (2.25, 2.41)**	**100**

–3.04   0   3.04

Figure 2 Pooled overall response rate (double arcsine form) of rituximab-based combinations in patients with Waldenström macroglobulinemia. The diamond indicates the estimated overall response rate and their corresponding 95% CI (double arcsine form after Freeman–Tukey transformation).
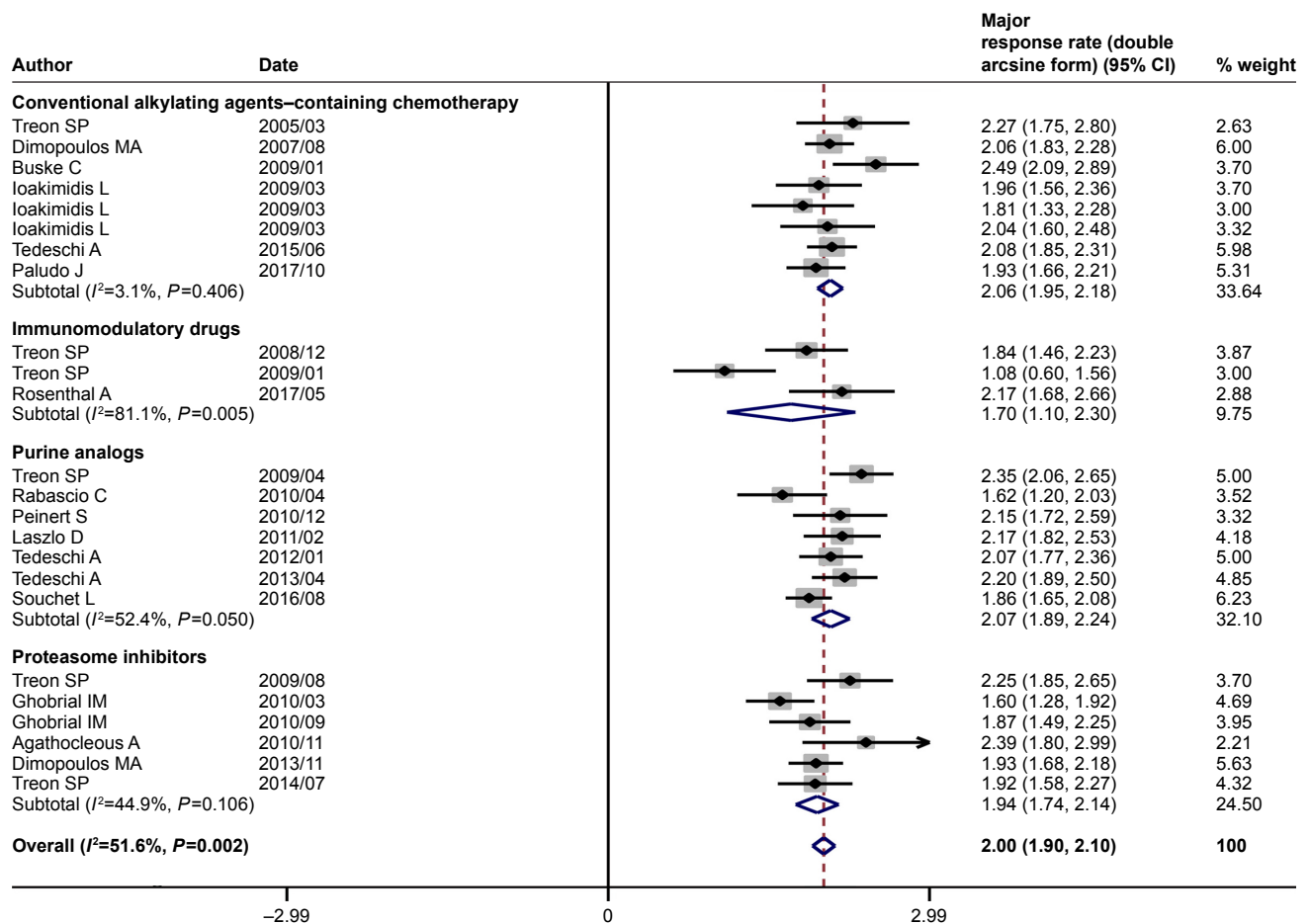**Note:** Weights are from random-effects analysis.

CI: 81%–87%), an MRR of 71% (95% CI: 66%–75%), and a CRR of 7% (95% CI: 5%–10%). The subgroup analysis indicated the response outcomes of rituximab plus agents with different mechanisms of action. Rituximab plus conventional alkylating agents–containing chemotherapy (subgroup A) yielded an ORR of 86% (95% CI: 81%–89%), an MRR of 74% (95% CI: 69%–79%) and a CRR of 8% (95% CI: 4%–14%). Rituximab plus purine analog (subgroup B) resulted in an ORR of 85% (95% CI: 79%–89%), an MRR of 74% (95% CI: 66%–81%), and a CRR of 9% (95% CI: 4%–15%). Rituximab plus proteasome inhibitor (subgroup C) resulted in an ORR of 86% (95% CI: 81%–90%), an MRR of 68% (95% CI: 58%–77%), and a CRR of 7% (95% CI: 3%–11%). Rituximab plus immunomodulatory drug (subgroup D) attained relatively lower response rates, with an ORR of 67% (95% CI: 51%–81%), an MRR of 56% (95% CI: 27%–83%), and a CRR of 5% (95% CI: 1%–12%). As demonstrated in Table 3, there existed no statistically significant differences in ORR, MRR, and CRR between subgroups A and B, subgroups A

and C, and subgroups B and C. The response outcomes derived from subgroup A have statistical difference to those of subgroup D in ORR (86% vs 67%, P=0.001) and MRR (74% vs 56%, P=0.002). Likewise, the response outcomes derived from subgroup B have statistical difference to those of subgroup D in ORR (85% vs 67%, P=0.002) and MRR (74% vs 56%, P=0.006). The ORR was statistically different between subgroups C and D (86% vs 67%, P=0.001). All the four subgroups resulted in a roughly similar CRR.

Hematological toxicities

We also performed the pooled analysis to explore the hematological adverse events of rituximab-based combination therapy in WM patients. Given the rare occurrence or even zero event of high-grade toxicities, Freeman–Tukey double arcsine transformation was also required for pooling hematological adverse events, as demonstrated in Figure 6A–C. Then, the pooled results were transformed back to their original form as summarized in Figure 6D. The most frequent

Author	Date		Major response rate (double arcsine form) (95% CI)	% weight
Conventional alkylating agents–containing chemotherapy				
Treon SP	2005/03		2.27 (1.75, 2.80)	2.63
Dimopoulos MA	2007/08		2.06 (1.83, 2.28)	6.00
Buske C	2009/01		2.49 (2.09, 2.89)	3.70
Ioakimidis L	2009/03		1.96 (1.56, 2.36)	3.70
Ioakimidis L	2009/03		1.81 (1.33, 2.28)	3.00
Ioakimidis L	2009/03		2.04 (1.60, 2.48)	3.32
Tedeschi A	2015/06		2.08 (1.85, 2.31)	5.98
Paludo J	2017/10		1.93 (1.66, 2.21)	5.31
Subtotal (I^2=3.1%, P=0.406)			2.06 (1.95, 2.18)	33.64
Immunomodulatory drugs				
Treon SP	2008/12		1.84 (1.46, 2.23)	3.87
Treon SP	2009/01		1.08 (0.60, 1.56)	3.00
Rosenthal A	2017/05		2.17 (1.68, 2.66)	2.88
Subtotal (I^2=81.1%, P=0.005)			1.70 (1.10, 2.30)	9.75
Purine analogs				
Treon SP	2009/04		2.35 (2.06, 2.65)	5.00
Rabascio C	2010/04		1.62 (1.20, 2.03)	3.52
Peinert S	2010/12		2.15 (1.72, 2.59)	3.32
Laszlo D	2011/02		2.17 (1.82, 2.53)	4.18
Tedeschi A	2012/01		2.07 (1.77, 2.36)	5.00
Tedeschi A	2013/04		2.20 (1.89, 2.50)	4.85
Souchet L	2016/08		1.86 (1.65, 2.08)	6.23
Subtotal (I^2=52.4%, P=0.050)			2.07 (1.89, 2.24)	32.10
Proteasome inhibitors				
Treon SP	2009/08		2.25 (1.85, 2.65)	3.70
Ghobrial IM	2010/03		1.60 (1.28, 1.92)	4.69
Ghobrial IM	2010/09		1.87 (1.49, 2.25)	3.95
Agathocleous A	2010/11		2.39 (1.80, 2.99)	2.21
Dimopoulos MA	2013/11		1.93 (1.68, 2.18)	5.63
Treon SP	2014/07		1.92 (1.58, 2.27)	4.32
Subtotal (I^2=44.9%, P=0.106)			1.94 (1.74, 2.14)	24.50
Overall (I^2=51.6%, P=0.002)			**2.00 (1.90, 2.10)**	**100**

−2.99　　　0　　　2.99

Figure 3 Pooled major response rate (double arcsine form) of rituximab-based combinations in patients with Waldenström macroglobulinemia. The diamond indicates the estimated major response rate and their corresponding 95% CI (double arcsine form after Freeman–Tukey transformation).
Note: Weights are from random-effects analysis.

grade ≥3 hematological adverse events consisted primarily of neutropenia (33%, 95% CI: 17%–52%), thrombocytopenia (7%, 95% CI: 3%–11%), and anemia (5%, 95% CI: 3%–9%).
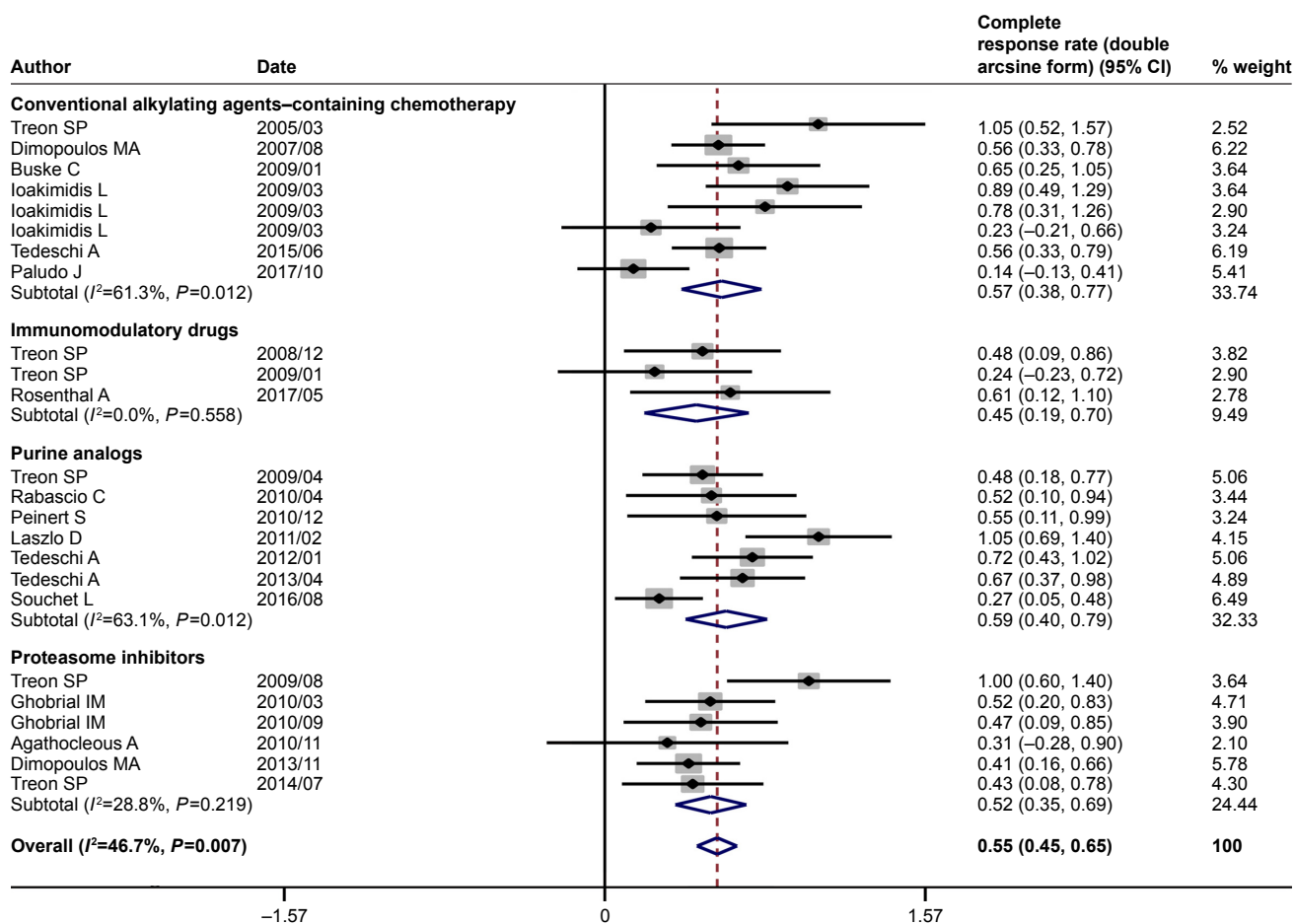
Publication bias

As indicated in Table 4, there was no evident publication bias detected by Egger's test and Begg's test for all the meta-analysis outcomes.

Discussion

Several clinical trials examined the efficacy of rituximab monotherapy for WM, including standard rituximab monotherapy (four weekly rituximab infusions) and an extended one (extra four weekly infusions at weeks 12–16 after standard therapy). Standard rituximab administration yielded an ORR of 40% and an MRR of 30%. The extended regimen produced an ORR of 60% and an MRR of 40%. VGPR and CR were scarcely observed in both the schedules. These studies indicated that rituximab monotherapy exhibited a moderate effect against WM.[36–38] Rituximab monotherapy often resulted in the much more frequent occurrence of serum IgM flare, the exacerbation of symptomatic hyperviscosity, and an increased risk of IgM-related morbidities.[10,39,40] Therefore, an increasing number of studies focusing on the addition of agents with different mechanisms of action to rituximab have been conducted in an attempt to explore more effective and better-tolerated combination regimens.

To the best of our knowledge, this pooled analysis is the first one to explore the efficacy and safety of rituximab-based combination therapy in patients with symptomatic WM. We have every reason to believe that our pooled analysis can provide a comprehensive perspective and facilitate individual observation of each single study with a relatively small sample size. As previously indicated in Figure 5 and Table 3, rituximab-based combinations (with alkylating agents, purine analogs, proteasome inhibitors, and immunomodulatory drugs) produced an encouraging pooled ORR of 84% and an MRR of 71%, acting as the mainstay for the treatment of

Author	Date		Complete response rate (double arcsine form) (95% CI)	% weight
Conventional alkylating agents–containing chemotherapy				
Treon SP	2005/03		1.05 (0.52, 1.57)	2.52
Dimopoulos MA	2007/08		0.56 (0.33, 0.78)	6.22
Buske C	2009/01		0.65 (0.25, 1.05)	3.64
Ioakimidis L	2009/03		0.89 (0.49, 1.29)	3.64
Ioakimidis L	2009/03		0.78 (0.31, 1.26)	2.90
Ioakimidis L	2009/03		0.23 (−0.21, 0.66)	3.24
Tedeschi A	2015/06		0.56 (0.33, 0.79)	6.19
Paludo J	2017/10		0.14 (−0.13, 0.41)	5.41
Subtotal (I^2=61.3%, P=0.012)			0.57 (0.38, 0.77)	33.74
Immunomodulatory drugs				
Treon SP	2008/12		0.48 (0.09, 0.86)	3.82
Treon SP	2009/01		0.24 (−0.23, 0.72)	2.90
Rosenthal A	2017/05		0.61 (0.12, 1.10)	2.78
Subtotal (I^2=0.0%, P=0.558)			0.45 (0.19, 0.70)	9.49
Purine analogs				
Treon SP	2009/04		0.48 (0.18, 0.77)	5.06
Rabascio C	2010/04		0.52 (0.10, 0.94)	3.44
Peinert S	2010/12		0.55 (0.11, 0.99)	3.24
Laszlo D	2011/02		1.05 (0.69, 1.40)	4.15
Tedeschi A	2012/01		0.72 (0.43, 1.02)	5.06
Tedeschi A	2013/04		0.67 (0.37, 0.98)	4.89
Souchet L	2016/08		0.27 (0.05, 0.48)	6.49
Subtotal (I^2=63.1%, P=0.012)			0.59 (0.40, 0.79)	32.33
Proteasome inhibitors				
Treon SP	2009/08		1.00 (0.60, 1.40)	3.64
Ghobrial IM	2010/03		0.52 (0.20, 0.83)	4.71
Ghobrial IM	2010/09		0.47 (0.09, 0.85)	3.90
Agathocleous A	2010/11		0.31 (−0.28, 0.90)	2.10
Dimopoulos MA	2013/11		0.41 (0.16, 0.66)	5.78
Treon SP	2014/07		0.43 (0.08, 0.78)	4.30
Subtotal (I^2=28.8%, P=0.219)			0.52 (0.35, 0.69)	24.44
Overall (I^2=46.7%, P=0.007)			**0.55 (0.45, 0.65)**	**100**

−1.57   0   1.57

Figure 4 Pooled complete response rate (double arcsine form) of rituximab-based combinations in patients with Waldenström macroglobulinemia. The diamond indicates the estimated complete response rate and their corresponding 95% CI (double arcsine form after Freeman–Tukey transformation).
Note: Weights are from random-effects analysis.

WM. Probably due to the indolent nature of WM, all the four different subgroups achieved low CRRs, with no statistically significant differences among each other (all P>0.05). Rituximab combined with immunomodulatory drug revealed an evidently lower ORR as compared with rituximab plus alkylating agent–containing chemotherapy (67% vs 86%, P=0.001), rituximab plus purine analog (67% vs 85%, P=0.002), and rituximab plus proteasome inhibitor (67% vs 86%, P=0.001). Meanwhile, rituximab combined with immunomodulatory drug also yielded a lower MRR as compared with rituximab plus alkylating agent–containing chemotherapy (56% vs 74%, P=0.002) and rituximab plus purine analog (56% vs 74%, P=0.006). However, the differences in ORR and MRR among the rest of the three different subgroups were statistically insignificant (all P>0.05). The result mentioned above is consistent with the fact that rituximab combined with thalidomide or lenalidomide was not recommended anymore and had been deleted from National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology

(NCCN Guidelines®): Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma (Version 1.2018).

As for toxicities, we only pooled the rates of commonly observed grade ≥3 hematological adverse events including neutropenia (33%), thrombocytopenia (7%), and anemia (5%). We did not take nonhematological toxicity into consideration in that most of the included studies reported only a minor proportion of patients suffering from various grade ≥3 nonhematological adverse events. We did not also analyze infusion-related reactions caused by rituximab. Infusion-related reactions of rituximab were commonly observed during the first infusion, which were primarily restricted to grade ≤2 adverse events including transient dyspnea and hypertension, angioedema, bronchospasm, cough, pyrexia, chills, rash, and vomiting.[41] When a patient suffers from infusion-related reactions, the infusion should be slowed down or temporarily suspended. Concurrent administration of antihistamines and corticosteroids also serves as a good therapeutic or prophylactic approach.[42,43] Besides, the number
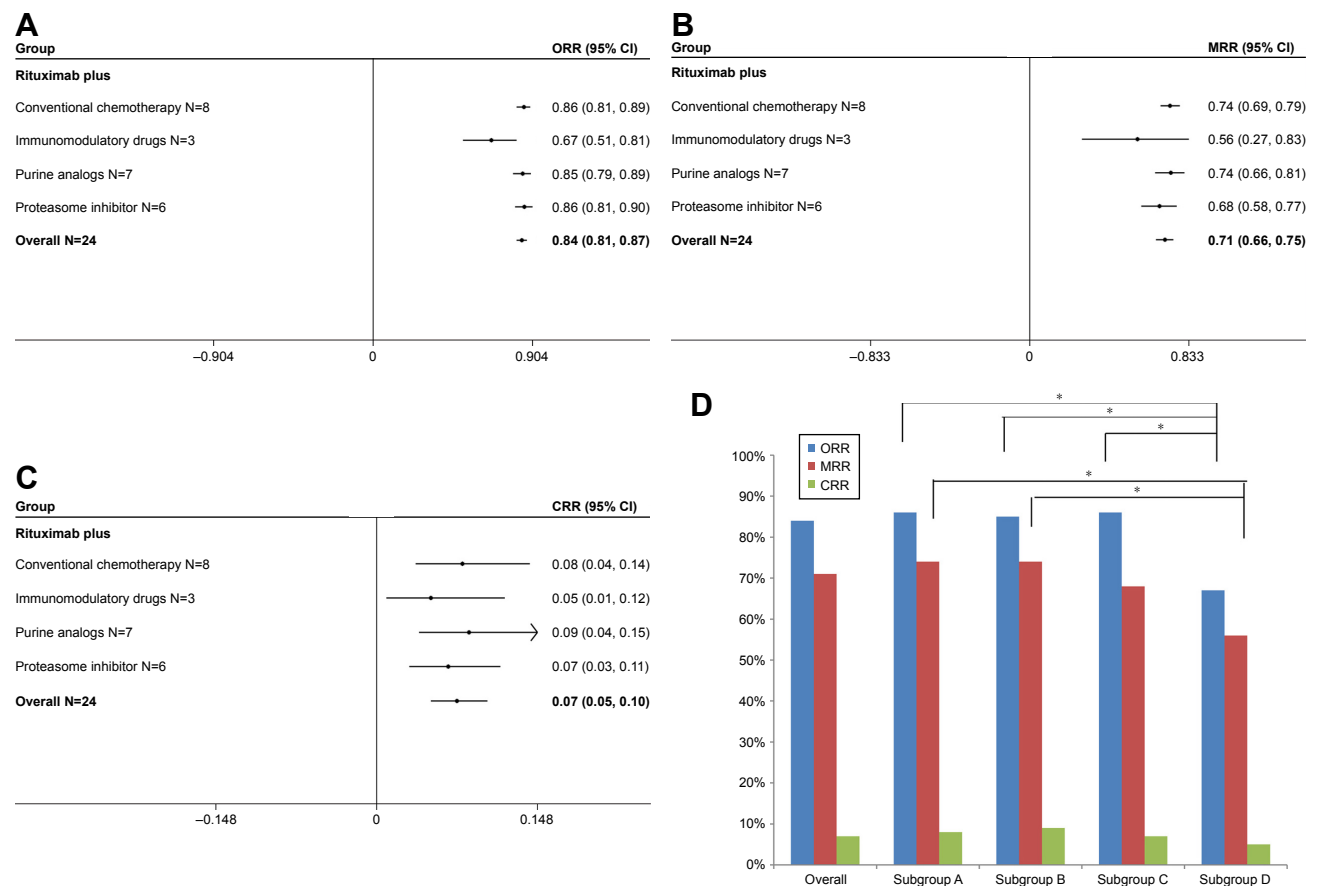
Figure 5 Summary of pooled response rate (original form) of rituximab-based combinations and different subgroups in patients with Waldenström macroglobulinemia. (**A**) Pooled ORR. (**B**) Pooled MRR. (**C**) Pooled CRR. (**D**) The percentage bar diagram for overall and subgroups A, B, C, and D for ORR, CRR, and MRR. Subgroup A represents rituximab plus conventional alkylating agents–containing chemotherapy group; subgroup B represents rituximab plus purine analog group; subgroup C represents rituximab plus proteasome inhibitor group; and subgroup D represents rituximab plus immunomodulatory drug group. *$P<0.007143$. The diamond indicates the estimated response rate and their corresponding 95% CI (original form).
Note: Weights are from random-effects analysis.
Abbreviations: CRR, complete response rate; MRR, major response rate; ORR, overall response rate.

of patients who were intolerant to rituximab mainly due to infusion-related reactions was very small in most of the included studies. Ofatumumab, a fully human monoclonal anti-CD20 antibody, may be a successful substitute for rituximab to mitigate severe infusion-related reactions. IgM flare phenomenon is also commonly observed with the use of ofatumumab. Therefore, serum IgM monitoring is still required.[44–46]

Although only a small subset of patients achieved CR or VGPR in almost all the included studies, WM follows a protracted and indolent course with a median survival of 10 years. It is not uncommon to acquire significant symptomatic amelioration even with a minor response.[47] In other words, mere minor response may be associated with encouraging clinical benefit. Therefore, higher priority should be accorded to disease or symptom control for the treatment of WM, in which patients do not suffer from severe disease-related symptoms and "symptom-free survival" duration

may prolong and last for several years despite the presence of bone marrow involvement and/or high serum IgM concentration.[48,49] According to individual patient characteristics and clinical manifestations, therapeutic regimens that are oriented toward a sustained disease control and the prevention of end-organ damage with minimal toxicity rather than a hematological CR are strongly recommended strategies for the initial treatment of WM. The therapeutic algorithm is summarized as follows.[5,11,50–54] Rituximab + bendamustine (BR) or rituximab + cyclophosphamide + dexamethasone (RCD) are primary choices for patients with WM-induced cytopenias or moderate to severe organomegaly or bulky lymphadenopathy. For patients with severe symptomatic hyperviscosity, cryoglobulinemia, or cold agglutinemia, preemptive plasmapheresis before drug administration is required, especially for those with serum IgM level of at least 4,000 mg/dL to evade IgM flare. Then, the administration of weekly subcutaneous bortezomib as a single agent is

**Table 3** Comparison between different subgroups of ORR, MRR, and CRR

	ORR	P-value	MRR	P-value	CRR	P-value
Subgroup A vs subgroup B	86% vs 85%	0.770	74% vs 74%	0.875	8% vs 9%	0.905
Subgroup A vs subgroup C	86% vs 86%	0.878	74% vs 68%	0.118	8% vs 7%	0.553
Subgroup A vs subgroup D	86% vs 67%	0.001	74% vs 56%	0.002	8% vs 5%	0.305
Subgroup B vs subgroup C	85% vs 86%	0.681	74% vs 68%	0.158	9% vs 7%	0.488
Subgroup B vs subgroup D	85% vs 67%	0.002	74% vs 56%	0.006	9% vs 5%	0.280
Subgroup C vs subgroup D	86% vs 67%	0.001	68% vs 56%	0.167	7% vs 5%	0.495

Notes: Subgroup A represents rituximab plus conventional alkylating agents–containing chemotherapy group, subgroup B represents rituximab plus purine analog group, subgroup C represents rituximab plus proteasome inhibitor group, and subgroup D represents rituximab plus immunomodulatory drug group. Comparisons between the four different subgroups were performed with partitions of Pearson's chi-squared test by which a two-tailed P-value of <0.007143 was deemed statistically significant.
Abbreviations: CRR, complete response rate; MRR, major response rate; ORR, overall response rate.

preferred before rituximab infusion (bortezomib + rituximab + dexamethasone), and thus serum IgM level may decrease instantly. Fludarabine + cyclophosphamide + rituximab regimen is also effective but of high myelotoxicity. For patients with paraprotein-related neuropathy, plasmapheresis is also needed but should not be employed as a permanent modality. RCD or FR or BR is effective, and combination regimens that

contain neurotoxic agents such as bortezomib, thalidomide, and vincristine should be avoided. Carfilzomib, a second-generation proteasome inhibitor, which functions by binding irreversibly to active sites of 20S proteasome, is of low neurotoxicity. The combination of carfilzomib, rituximab, and dexamethasone (CaRD) in previously untreated patients achieved an ORR of 87% with no grade $\geq$3 neuropathy
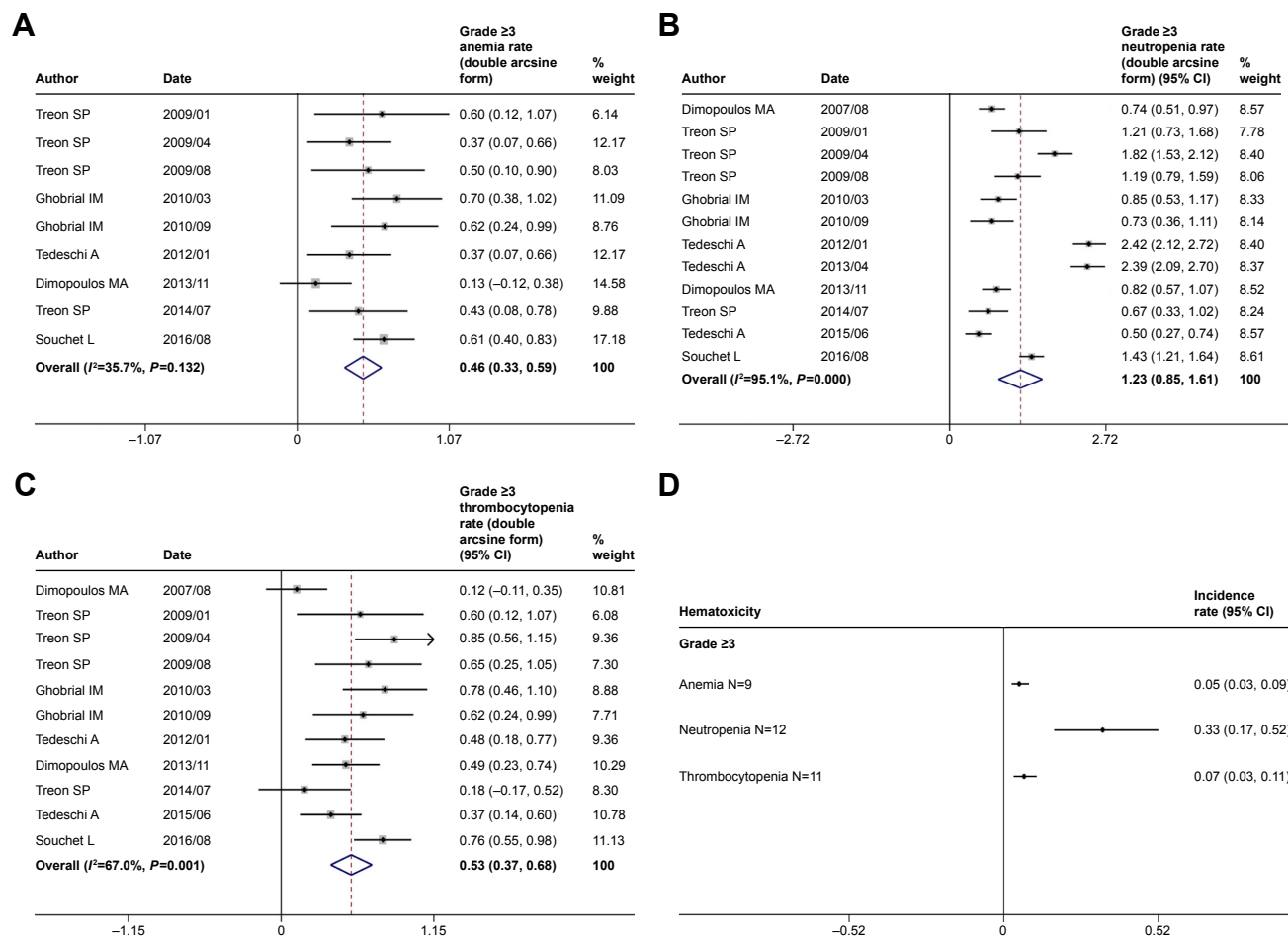
Figure 6 Pooled rates of grade $\geq$3 hematological adverse events of rituximab-based combinations. Rates (double arcsine form after Freeman–Tukey transformation) of (**A**) anemia, (**B**) neutropenia, (**C**) thrombocytopenia, and (**D**) summary of grade $\geq$3 anemia, neutropenia, and thrombocytopenia (original form).
Note: Weights are from random-effects analysis.

Table 4 Publication bias assessment of the pooled results

Pooled results	P-value	
	Egger's test	Begg's test
Complete response rate	0.122	0.308
Major response rate	0.931	0.602
Overall response rate	0.836	0.502
Grade ≥3 anemia	0.638	0.404
Grade ≥3 neutropenia	0.654	0.492
Grade ≥3 thrombocytopenia	0.595	0.815

observed. Importantly, the response status was not influenced by *MYD88* and *CXCR4* gene mutations.[31] CaRD and bortezomib + rituximab + dexamethasone regimens are also preferably recommended in WM patients with IgM-associated light-chain amyloidosis and renal dysfunction. Bing–Neel syndrome is a rare WM complication featuring the involvement of lymphoplasmacytic cells in the central nervous system, for which an intrathecal injection is required. Combinations that contain fludarabine or bendamustine may play a critical role in Bing–Neel syndrome treatment due to their strong blood–brain barrier permeability.[55,56]

In some combination regimens, rituximab infusion is postponed until the second cycle so as to bring the effect of cytotoxic therapy into full play, thus decreasing IgM level and minimizing the risk of rituximab-induced hyperviscosity syndrome. Although the RCD regimen was effective with minimal myelotoxicity, the median time to response was 4.1 months, indicating that RCD regimen was unsuitable for a rapid disease control.[15,57] Besides, the response to rituximab may vary among individuals, probably due to the influence exerted by *FCGR3A* gene polymorphism.[58] For young patients who are eligible for autologous stem cell transplantation, the administration of purine analogs should be avoided as an initial therapy in that such kind of agents have a strong myelosuppressive activity and are toxic to stem cells, thus impeding the harvest of stem cells. Of course, it is a good alternative that stem cells should be collected before fludarabine administration. The use of fludarabine has also close correlation with severe cytopenias, autoimmune hemolytic anemia, and an increased risk of secondary malignancies such as myelodysplastic syndrome or acute myeloid leukemia,[59] while rituximab in combination with cladribine yielded an ORR of nearly 90% with more modest toxicity as compared with fludarabine.[60] It is noteworthy that plasmapheresis alone, acting as an urgent measure taken to decrease high circulating IgM rapidly, is far from efficacious for a long-term disease control and must be followed by cytoreductive therapies that aim at killing the IgM-producing lymphoplasmacytic cells.[61]

Ibrutinib, a kind of Bruton's tyrosine kinase (BTK) inhibitor, abrogates the abnormal activation of nuclear factor-κB signaling pathway by disrupting the interactions between the mutated *MYD88* (*Leu265Pro*) protein and BTK.[62] A phase III clinical trial evaluated the efficacy and safety of ibrutinib in patients who are refractory to rituximab-based combination therapy. Of 31 patients who were evaluated, 28 (90%) patients achieved overall response and 22 (71%) patients obtained major response. Common grade 3 or worse hematological toxicity included neutropenia in 4 (13%) patients, anemia in 2 (6%), and thrombocytopenia in 2 (6%) patients.[63] It is well established that recurrent somatic mutations of the *MYD88* gene (*MYD88 Leu265Pro*) and *CXCR4* gene (*CXCR4 WHIM*) were observed in ~90% and 40% of WM patients, respectively. Ibrutinib monotherapy was highly effective in patients with an MYD88 mutation. While, *CXCR4WHIM* mutations potentiate resistance to ibrutinib.[7,64] The emergence of BTK inhibitors, such as ibrutinib, zanubrutinib, and acalabrutinib, may provide more promising options for WM treatment. However, the cost of ibrutinib is prohibitive. The efficacy has to be weighed against the cost. Besides, clinical data of such agents in combination with other drugs are inadequate.

There existed some drawbacks in our meta-analysis. First, we were unable to pool progression-free survival (PFS) and overall survival (OS) outcomes despite the fact that PFS and OS might be more indicative of the actual clinical benefit. The reasons are as follows: Different researchers defined PFS and explained PFS outcomes in quite distinct ways, including median PFS, median duration of response, and time to progression. Besides, the duration of follow-up varied among the included studies, and PFS or OS rates were reported at different follow-up times. Some included studies did not even report PFS or OS outcomes probably due to the indolence of WM. Second, the pooled calculations of all the rates were based on the published data instead of individual patient data, and the patient baseline characteristics were broadly divergent among studies. Therefore, response rates could not be synthesized according to the subgroups of age, gender, previous therapy, *MYD88* and *CXCR4* gene mutation status, serum IgM level, bone marrow involvement, clinical manifestations, and other risk stratification factors. Third, many included original studies did not differentiate newly diagnosed WM patients who had no prior therapies from patients with relapsed or refractory WM. Therefore, our meta-analysis failed to make a clear distinction. Fourth, the agents, dosage, cycles, and routes of administration within the same subgroup were not utterly consistent. Last, information

bias was inevitable because six retrospective studies were also included in our meta-analysis.

Conclusion

In summary, our meta-analysis indicated that rituximab-based chemoimmunotherapy is highly effective with tolerable toxicity, serving as the backbone of both the initial and salvage treatment in a relatively economical manner. More importantly, we should choose the most suitable combination regimen in accordance with the individual patient's clinical features and related comorbidities.

Data availability statement

Our meta-analysis overviewed and extracted data from the previously published articles, all of which are cited in the manuscript and can be found online. The processed data are available from the corresponding author upon request.

Disclosure

All authors report no conflicts of interest in this work.

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