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The efficacy and safety of triplet regimens based on pomalidomide and dexamethasone for treatment of relapsed/refractory multiple myeloma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Triplet regimens based on pomalidomide and dexamethasone have been applied to treat relapsed/refractory multiple myeloma, but the safety and efficacy are not yet very clear. This meta-analysis aimed at comparing the safety and efficacy of different triplet therapies and analyzing the best therapy regimen.

MATERIALS AND METHODS: A comprehensive literature search identified a total of 615 studies, and 22 studies assessing 1,889 subjects met the inclusion criteria of this meta: phase II/III trial, over 2 median lines of prior therapy, and detailed efficacy outcomes like overall response rate (ORR), overall survival, and progression-free survival (PFS). All statistical analyses were performed by Revman version 5.3, and the heterogeneity was tested by I^2 (25% indicating low heterogeneity, 50% moderate, and 75% high). For those with less heterogeneity, fixed-effect model was used. With a significant high heterogeneity, a random-effect model was used.

RESULTS: Pooled analysis showed ORR 66.2% across all triplet regimens based on pomalidomide and dexamethasone. Among all triplet regimens, therapy containing bortezomib showed the highest ORR (90.3%), and the one containing elotuzumab showed the lowest ORR (41.2%). The pooled ORRs for the remaining treatment regimens are as follows: cyclophosphamide (70.1%), isatuximab (66.3%), daratumumab (61.2%), clarithromycin (60.0%), pembrolizumab (47.3%). A total of 21 adverse events appeared in the included studies, with neutropenia being the highest incidence of hematologic adverse events (32.1%) and cough being the highest incidence of non-hematologic adverse events (43.3.%).

CONCLUSIONS: Three-drug regimens based on pomalidomide and dexamethasone could yield excellent overall response rate to relapsed/refractory multiple myeloma, but there are still various adverse events; therefore, consequent studies should address these adverse events.

Key Words:
Multiple myeloma, Triplet regimen, Overall response, Efficacy, Adverse events.

Introduction

Multiple myeloma (MM) is a malignant hematological tumor with clonal proliferation of plasma cells in the bone marrow and/or peripheral sites. It is also the second most common hematological malignancy, accounting for 20% of deaths from hematological malignancies[1,2]. MM is characterized by the presence of monoclonal immunoglobulins in the blood or urine, causing anemia, renal insufficiency, extensive bone destruction, hypercalcemia, and recurrent severe infections[3,4]. While research on multiple myeloma has achieved good and encouraging progress over the past few decades, the prognosis of MM remains very poor because of the heterogeneity of clones and the complexity of the genome, and it remains largely considered as an incurable disease. The widespread use of immunomodulators drug (IMiD) and proteasome inhibitors (PI) have prompted the treatment of MM, with complete remission increasing from about 5% to more than 30% and overall survival prolonging from less than 3 years to 5 years[5-7]. Although the introduction of several new drugs has led to improvements, almost all MM patients eventually become relapsed/refractory MM (RRMM). Immune system in RRMM becomes increasingly dysregulated with each treatment, which will lead to aggressive and resistant disease, so the treatment of RRMM remains challenging[8,9].

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It is extremely important to study multi-drug combination regimens. Pomalidomide is a third-generation IMiD that mediates the proteasomal degradation of transcription factors by binding to the protein Cereblon in the E3 ubiquitin ligase complex, which exerts powerful, direct antitumor and immune-potentiating effects[10-12]. Although its chemical structure is like that of other IMiDs (thalidomide and lenalidomide), pomalidomide has unique antitumor, antiangiogenic, and immunomodulatory properties[13-15]. Combination therapy with other drugs with different mechanisms improves the prognosis of patients with RRMM, and multi-drug combination regimens provide a feasible approach to overcome the heterogeneity and drug resistance of RRMM and preserve immune system function.

Numerous studies[16,17] have shown a synergistic anti-proliferative activity of pomalidomide with dexamethasone in RRMM patients resistant to lenalidomide. The combination of pomalidomide and dexamethasone has been approved in the United States, Canada, and the European Union for the treatment of RRMM patients. Some clinical trials have used triplet regimens based on pomalidomide and dexamethasone for the treatment of RRMM[18,19]. However, the overall response rate (ORR) of these triplet regimens is not very clear, and most of these studies are clinical trials with small sample sizes, thus the clinical trial results cannot determine the efficacy of the triplet regimens for RRMM. At the same time, the safety and side effects of these triplet regimens also lack summary reports[20,21]. Here, we conducted a meta-analysis of clinical trials to summarize the efficacy and safety of triplet regimens based on pomalidomide and dexamethasone for patients with RRMM.

Materials and Methods

Strategy of Literature Search

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guideline recommended by PRISMA, the literature search in PubMed, MEDLINE, EMBASE, SCOPUS, Cochrane Library and other databases was conducted in May 2021, and the literature language was limited to English. Primary search terms included ("multiple myeloma" OR "MM") AND "pomalidomide" AND "dexamethasone". We included full text of clinical trials without any restrictions concerning age, gender or other factors.

Inclusion and Exclusion Criteria

The published studies were included in this meta-analysis according to the following criteria: (1) patients with RRMM treated with pomalidomide in combination with dexamethasone; (2) the clinical trials focused on phase II or III; (3) all studies had clear outcome measures, including but not limited to ORR; (4) The study included a description of the incidence of related adverse events. Additionally, we excluded the following literatures: (1) the types of literatures were case report and review article; (2) the studies recruited less than 10 patients; (3) the studies lack of outcome measures. Only most recent studies were included when same publications were based on the same population.

Data Extraction

All literatures were carefully screened according to the above criteria. All study data included in this meta-analysis were independently extracted by two experienced reviewers using a standardized data extraction form to avoid selection bias. Disagreements between the two reviewers were resolved by consensus or consultation with a third reviewer. The following information was extracted from each included study: (1) the name of first author; (2) published year of study; (3) the number of patients included in the study; (4) mean age of subjects; (5) therapy schedule based on pomalidomide and dexamethasone; (6) related adverse events; (7) progression-free survival; (8) international staging system (ISS); (9) median lines of prior therapy; (10) overall response rate (95% CI, confidence interval).

Statistical Analysis

All data analysis was performed using RevMan 5.3 software (Review Manager Web, The Cochrane collaboration, Copenhagen). I^2 index was applied to calculate the degree of heterogeneity of included studies (25% indicating low heterogeneity, 50% moderate, and 75% high). For those with less heterogeneity, fixed-effect model was used for meta-analysis. If there was significant high heterogeneity, a random-effect model was used to combine the size of effect size in each group. Stratified analysis was performed by dividing the study into treatment groups, forest plots were generated to report the study results, the pooled results are represented by diamonds, and the 95% CI by the lines on both sides of the square. The significance level was set at $p<0.05$.

Results

Literature Search Results

A total of 615 studies were included from the primary electronic database search: 470 from PubMed, 109 from EMBASE, and 36 from the Cochrane library and SCOPUS. After the assessment for duplicates, 68 studies were excluded. After title and abstract screening, 450 studies were excluded for obvious irrelevance, while 97 articles remained. After full-text screening, 75 studies were excluded because for not examining the disease of interest (n=47), no RRMM definition (n=18), being reviews or meta-analyses (n=7), or not about pomalidomide (n=3). Finally, 22 studies assessing 1,889 subjects were used for this meta-analysis. The study selection procedure is illustrated in Figure 1.

Main Characteristics of Eligible Studies

Included studies involved a total of 7 treatment regimens, the basic regimens were pomalidomide and dexamethasone (PD), other 7 regimen were cyclophosphamide, bortezomib, clarithromycin, daratumumab, elotuzumab, Isatuximab and pembrolizumab. The most common regimen was PD+ cyclophosphamide (Cyc) with 6 studies[5,6,14,22-24], followed by 4 trials each of following regimens: PD+ daratumumab (Dara)[15,25-27] and bortezomib (Bort)[20,21,28,29]; 3 trials each with the following regimens: PD+ pembrolizumab (Pem)[30-32]; 2 trials each with the following regimens: PD+ Isatuximab (Isa)[33,34] and Elotuzumab (Elo)[35,36], only one study[37] applied PD+ clarithromycin (Cla). All patients included in this study had over two prior lines of therapy, and the main previous refractory regimen was Lenalidomide (Table I).

Response Rate of Triplet Regimens

A total of 22 triplet regimens studies were included, and the pooled analysis of all studies showed an ORR of 66.2% in a random-effect model. The results of subgroup analysis indicated that PD+Bort had the highest ORR of 90.3%, and other ORR are as follows:PD+Cyc (70.1%), PD+Isa (66.3%), PD+Dara (61.2%), PD+Cla (60.0%), PD+Pem (47.3%) and PD+Elo (41.2%). Detailed data are presented in Figure 2.

Adverse Events

There are 21 adverse events which appeared in the included studies, and meta-analysis was per-

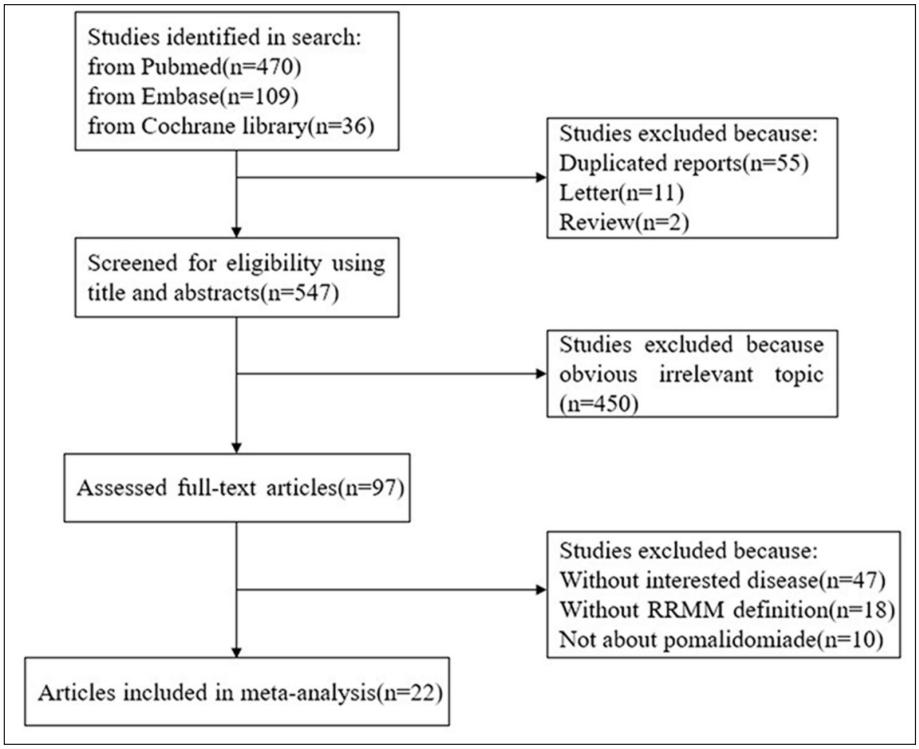

Figure 1. PRISMA flow chart of literature search and study selection.

Table I. Characteristics of included studies.

Authors	Year	No. of patients	Median age	Median lines of prior therapy	Refractory to previous regimen	ISS staging (1/2/3)	mSMART(High risk/Standard risk/ Unknown)	Regimen	ORR (%)	PFS (months)
Bringhen et al[33]	2021	154	68	3	Len	64/53/34	24/103/27	PD+Isatuximab	61.5	12.25
Dimopoulos et al[34]	2020	87	66	3	Len	45/32/7	11/63/13	PD+Isatuximab	67.8	12.7
Meletios et al[28]	2020	111	67	2	Len	65/33/13	58/18/35	PD+bortezomib	90	17.8
Paludo et al[29]	2017	50	65.5	2	Len	29/9/12	29/19/2	PD+bortezomib	86	13.7
Richardson et al[20]	2019	281	67	2	Len	149/85/47	137/61/73	PD+bortezomib	82.2	11.2
Sunami et al[21]	2020	12	72	2	Len	10/2	NR	PD+bortezomib	95	16.8
Mark et al[37]	2019	117	63	2	Len	42/37/26	39/28/11	PD+clarithromycin	60	19.2
Baz et al[22]	2016	34	65	≥2	Len	NR	7/8/9	PD+cyclophosphamide	65	12.1
Garderet et al[23]	2018	100	62	NR	NR	67/12/6	69/12/19	PD+cyclophosphamide	82	12.4
Lee et al[24]	2020	55	73.3	≥2	Len	13/30/8	11/33/11	PD+cyclophosphamide	58.2	7.6
Trudel et al[6]	2019	49	66	3	Len 80% Bort35%	29/53/18	9 high	PD+cyclophosphamide	76	6.5
Van Oekelen et al[5]	2020	33	65	3	Len	9/6/3	16/3/15	PD+cyclophosphamide	73	13.3
Soekojo et al[14]	2019	136	67	3	Len, Bort	51/46/35	NR	PD+cyclophosphamide	51.8	10.8
Nooka et al[25]	2019	34	65	3	Len 100%, Bort100%	11/15	26/8/-	PD+daratumumab	58.8	NR
Chari et al[26]	2017	103	64	4	PI+IMiD	NR	65/22/-	PD+daratumumab	60	8.8
Dimopoulos et al[27]	2021	151	67	4	Len 79% Pro 47%	68/50/33	39/64/-	PD+daratumumab	69	12.4
Siegel et al[15]	2020	112	66.5	3	Len	30/53/8	NR	PD+daratumumab	77.7	NR
Hose et al[35]	2020	22	61.5	4	Len	13/5/4	4/15/-	PD+elotuzumab	55	6.4
Dimopoulos et al[36]	2018	60	69	3	Bort100% Len 98%	53/7	NR	PD+elotuzumab	32	10.3
Badros et al[30]	2017	48	64	3	Bort100% Len 100%	NR	30/18/-	PD+pembrolizumab	50	15.6
Mateos et al[31]	2019	125	65	4	Bort 97% Len 95%	45/46/33	28/52/-	PD+pembrolizumab	34	7.8
Matsumoto et al[32]	2021	15	69	2	Bort100% Len 100%	5/8/2	7/8/-	PD+pembrolizumab	47	6.5

PD=Pomalidomide+Dexamethasone; Len=Lenalidomide; Pro=Proeasome; Bort=Bortezomib; ISS=International Staging System; ORR=Overall response rate; PFS=progression-free survival; Msmart=Mayo Stratification of Myeloma and Risk-adapted Therapy; PI=Proteasome inhibitor; IMiD=Immunomodulatory drug; NR=not reported

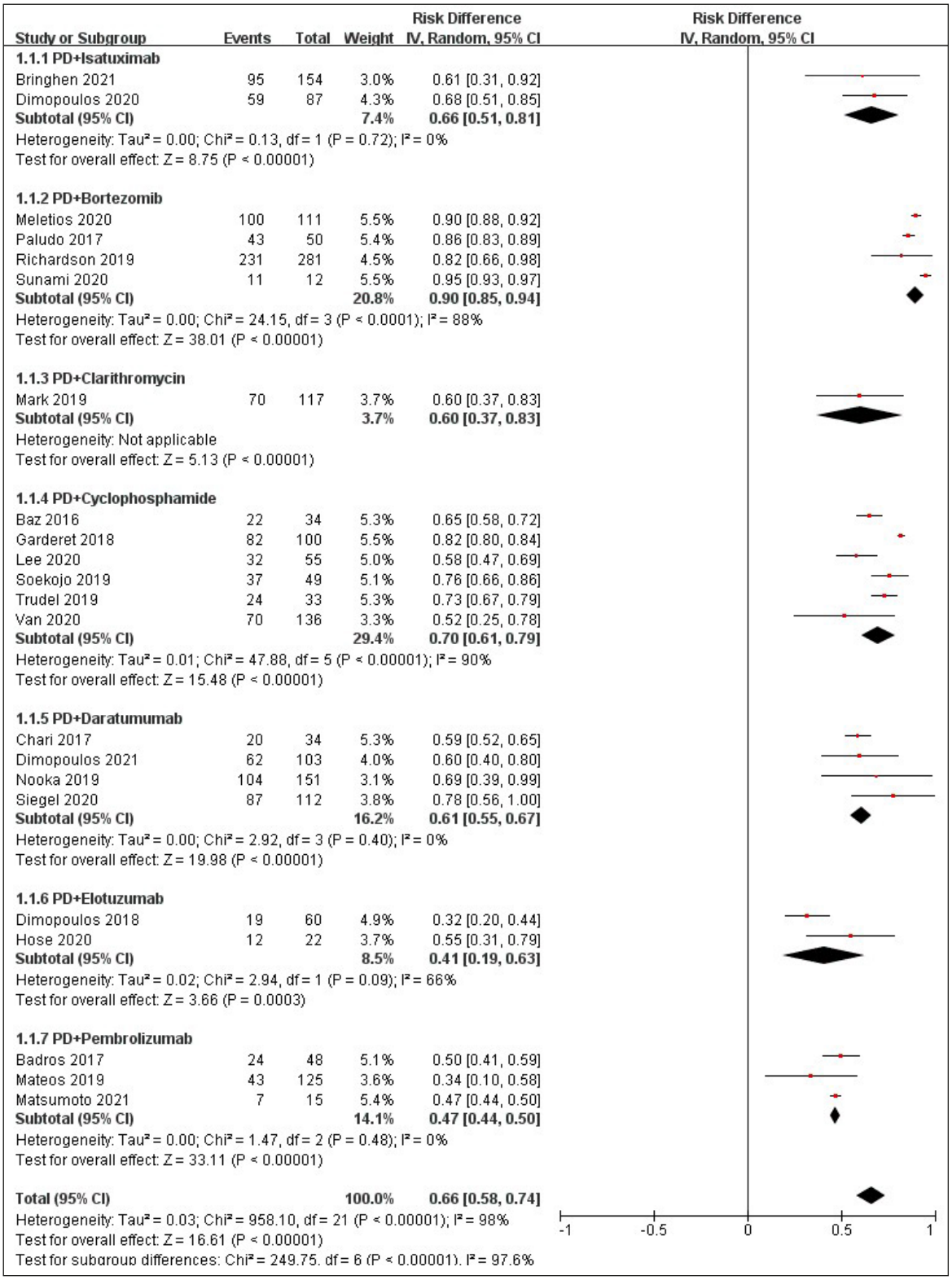

Figure 2. Forest plot of overall response rate for triplet regimens.

formed for all triplet regimens, with the highest incidence of hematologic AEs being neutropenia (32.1%) and the highest incidence of non-hematologic AEs being cough (43.3.%). 19 of 22 studies reported anemia as AEs, with 254 total cases (shown in Table II).

Publication Bias

All included studies reported overall response rate, so ORR was selected for publication bias analysis. Funnel plot results showed that there were no significant publication bias (Figure 3).

Therapy Schedule

Most studies set 28 days as a cycle, and the drugs were mainly administered by two routes: intravenous and by oral administration. Drug dose varied slightly in different studies[38-40] and some studies used body area to calculate the dose. Dexamethasone dose was halved to 20 mg in the elderly over 75 years of age in some trials[41,42]. due to some known AEs.

Discussion

RRMM is currently a major problem for clinicians because of drug resistance, poor treatment prognosis, and serious damage on patients' quality of life[25,29,43]. The insignificant therapeutic effects of previous drugs have prompted the development of the next generation of PI and IMiD, as well as regimen with new mechanisms of action (monoclonal antibodies), which further expands the therapeutic range of RRMM and provides a theoretical basis for the development of combinations of pomalidomide[44-46]. A variety of clinical studies[24,31,32,35,37] have used pomalidomide in combination with different drugs for the treatment of RRMM, and the purpose of using combination regimens is to enhance the therapeutic effect and reduce the occurrence of adverse events using the synergistic effects and non-overlapping toxic effects of different drugs.

At present, the dual combination of pomalidomide and dexamethasone is the most frequently used regimen, and relevant studies'[47,48] results show that the treatment effect using the triplet

Table II. Adverse events of triplet regimens.

Adverse events	Related studies	Total cases	Patients	Heterogeneity test		Pool rate	95%CI
				I^2	p		
Hematological adverse events							
Thrombocytopenia	18	416	1,378	85.2	<0.001	28.1	22.7-31.5
Anemia	19	254	1,425	93.1	<0.001	16.9	14.9-18.6
Neutropenia	15	378	1,109	90.8	<0.001	32.1	28.1-36.4
Leukopenia	17	198	1,372	89.3	<0.001	15.7	11.9-16.6
Lymphopenia	18	207	1,195	46.7	0.018	18.9	15.4-19.5
Non-hematological adverse events							
Fatigue	15	256	1,232	75.3	<0.001	19.3	18.1-22.5
Constipation	10	194	1,056	64.2	<0.001	17.2	16.7-20.1
Pyrexia	11	392	1,316	43.2	<0.001	27.3	26.4-30.7
Pneumonia	13	368	1,344	38.8	<0.001	26.1	25.1-28.3
Insomnia	14	347	1,217	79.2	<0.001	24.9	23.1-29.7
Diarrhea	9	288	1,008	40.7	<0.001	26.2	24.6-29.3
Upper respiratory tract infection	10	274	1,106	31.2	<0.001	22.3	21.9-25.4
Dyspnea	7	194	869	11.1	<0.001	24.6	21.6-25.8
Nausea	9	306	973	83.4	<0.001	29.5	28.9-33.1
Peripheral oedema	10	309	1,116	55.2	<0.001	26.3	25.1-28.5
Cough	13	549	1,218	83.1	<0.001	43.3	41.3-46.3
Muscle spasms	8	224	968	29.8	<0.001	22.4	21.0-24.2
Dizziness	11	352	1,203	18.4	<0.001	27.6	26.5-30.7
Headache	8	263	1,180	53.4	<0.001	21.9	20.1-24.5
Asthenia	5	118	693	19.9	<0.001	18.6	16.9-19.8
Back pain	6	199	849	10.4	<0.001	24.6	20.9-25.3

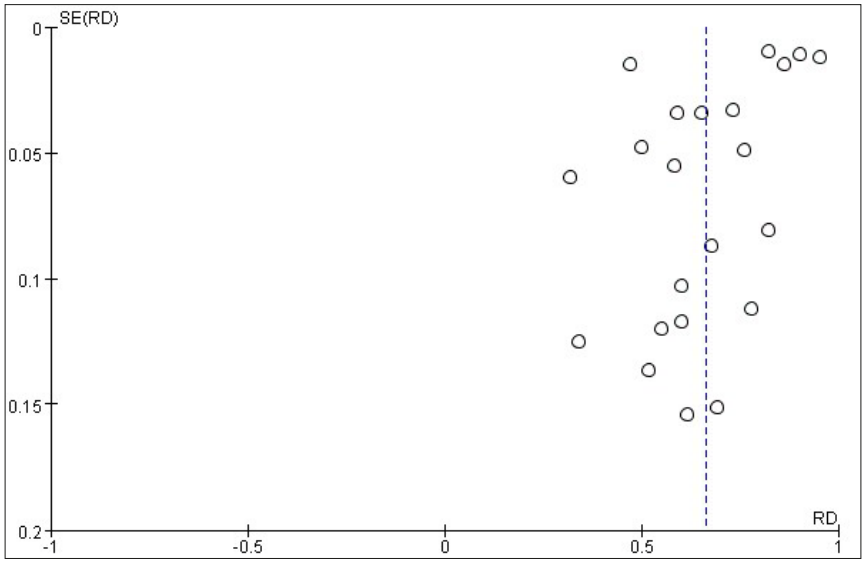

Figure 3. Funnel plot of overall response rate for triplet regimens.

regimens based on pomalidomide and dexamethasone is significantly better than the dual regimens. We performed this meta-analysis to study different triplet regimens, including 22 trials with 1,889 patients. The results indicates that the pooled ORR of triplet regimens is 66.2% and the PFS ranges between 6.4-19.2 months[23,27,34,36]. There is a total of 7 triplet regimens, of which pomalidomide, dexamethasone, and cyclophosphamide were the most used. The results of subgroup analysis show that the combination PD+Bort regimen (pooled ORR 90.3%) appeared to reflect better clinical efficacy, but the number of relevant clinical trials is small[26,28,49], and whether the study protocol has a definite better therapeutic effect needs to be verified by clinical trials with large samples.

Triplet regimens have been studied in previous studies, Richardson et al[19] conducted a related study on PVD in the treatment of RRMM, and the results showed that the ORR was 82.8%. Further analysis showed that the use of triplet regimens in RRMM patients with cytogenetics could lead to durable and deeper response, significantly improved PFS, and significantly reduced the risk of disease progression and death, indicating that this triple regimen may partially overcome the adverse prognosis of cytogenetic abnormalities, and that pomalidomide can induce response in RRMM patients with lenalidomide resistance[30,50]. The possible mechanism is that pomalidomide has a positive effect on the immune system of patients who fail to respond to lenalidomide by enhancing the activity and number of lenalidomide. Therefore, for patients with previous exposure to lenalidomide or ineffective lenalidomide, no drug class change is required[22,33].

In term of the therapy schedule, almost all trials[51,52] required multiple courses of medication, scholars[53] applied pomalidomide 4 mg daily as the baseline, but Paludo et al[29] did not endorse this option: they deemed that the dose of 4 mg did not induce better effect than 2 mg. The starting dose of dexamethasone in all studies was 40 mg, scholars[54] halved the dose to 20 mg for patients older than 75 for avoiding adverse events, only few studies[55] did not mention this.

While producing therapeutic effects, triplet therapy also induces AEs, the highest incidence of hematologic AEs is neutropenia (pooled rate 32.1%). There are many types of AEs, and the overall incidence of various AEs is high, indicating that the safety of the triplet regimens needs further study, and subsequent studies can focus on how to effectively manage adverse events.

Limitations

Limitations of our study are as follows: firstly, the small sample size of the included studies; secondly, conducting crossover trials to compare the optimal triplet regimens based on pomalidomide and dexamethasone for RRMM is imprecise because of heterogeneity between studies in different populations, differences in prior treatment routes, tolerance to prior therapy, ISS stage, cytogenetic risk stratification, and differences in dose

and timing. In addition, most analyzed studies[56,57] were not randomized controlled trials, and could have unclear risk of bias, including selection bias and reporting bias; therefore, the overall results of our final meta-analysis are not precise enough. However, in the absence of relevant randomized controlled studies, the results of this study provide a theoretical basis for the relative efficacy of different triplet regimens, and provide useful insights for the subsequent prospective research.

Conclusions

The results of this meta-analysis showed that three-drug regimens based on pomalidomide and dexamethasone could present excellent over response rate to relapsed/refractory multiple myeloma. However, some adverse events were also recorded in the trials, indicating that a small number of patients had side effects on this treatment regimen. More future studies with good quality are required to further address these adverse events, and to promote the application of triple therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

KL and YL selected the relevant studies and assessed the data. HX, XC and XZ contributed to the methodological framework. XL and CH revised the manuscript. All authors read and approved the final version of the manuscript.

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