

Treatment options for refractory/relapsed multiple myeloma: an updated evidence synthesis by network meta-analysis

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Background: The refractory/relapsed multiple myeloma (RRMM) remains a big clinical challenge, due to its biological and clinical complexity. Leading hematologists have performed many randomized controlled trials (RCTs) worldwide, and their findings were summarized in a recently published network meta-analysis (NMA) but with certain limitations.

Materials and methods: We performed an updated NMA of RCTs related to RRMM treatment, focusing on efficacy measures including the nonresponse rate (NRR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS). The PubMed database was searched. We extended the literature search strategy of a previous NMA to June 30, 2017 and included additional primary RCTs. The surface under the cumulative ranking curve (SUCRA) was calculated to rank the regimens. A weighted-average method was used to rank the regimens by summarizing SUCRAs across different outcome measures.

Results: Finally, a total of 24 RCTs were included in this updated NMA. According to the result, the combination of daratumumab, lenalidomide, and dexamethasone showed better efficacy than other regimens in terms of NRR, TTP, and PFS (NRR: odds ratio [OR] =0.046, 95% credible interval [CrI] =[0.024, 0.085]; TTP: hazard ratio [HR] =0.14, 95% CrI =[0.092, 0.2]; PFS: HR =0.12, 95% CrI =[0.077, 0.18], compared with dexamethasone singlet). The combination of ixazomib, lenalidomide, and dexamethasone showed better efficacy than other regimens in terms of OS (HR =0.30, 95% CrI =[0.17, 0.54], compared with dexamethasone). The combination of daratumumab, lenalidomide, and dexamethasone ranked first in terms of overall efficacy (weighted average of SUCRAs =0.920).

Conclusion: The combination of daratumumab, lenalidomide, and dexamethasone may currently be the most effective regimen in the population of RRMM patients. Triplet regimens containing daratumumab, ixazomib, carfilzomib, or elotumumab plus lenalidomide and dexamethasone can be recommended as first-line therapies for RRMM patients.

Keywords: multiple myeloma, refractory/relapsed, treatment regimens, efficacy, network meta-analysis

Introduction

Since the early 2000s, the introduction of newly developed agents has dramatically improved the outcome of patients with multiple myeloma. However, the refractory/relapsed multiple myeloma (RRMM) remains a big challenge, due to its biological and clinical complexity. In an attempt to find ways to conquer RRMM, world's leading hematologists have performed many randomized controlled trials (RCTs) worldwide. Recently, two research groups have tried to synthesize the results of these trials by network meta-analysis (NMA), a statistical analysis method by which a thorough

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comparison and ranking of all included treatment options is made possible.^{1,2} However, the two previous NMAs have certain limitations. To name a few, in the NMA by van Beurden-Tan et al,¹ important outcomes such as overall survival (OS) were left uninvestigated and the ranking information was not provided; and in the other NMA by Botta et al,² regimens were grouped into categories before comparison, some of which seem inappropriate and may cause bias and confusion. Besides, we found that several new RCTs and updated trial reports are available for a new NMA. Considering the above, we performed the present study to update the evidence and improve its quality using traditional NMA and a self-designed weighted average method to rank the regimens by summarizing results across various efficacy outcome measures.

Materials and methods

Outcome measures

This updated NMA focuses on early and long-term efficacy outcomes, including the nonresponse rate (NRR), time to progression (TTP), progression-free survival (PFS) and OS. Response rate was considered instead of NRR because its outcome event, that is, the absence of objective response to treatment, a negative indicator of treatment efficacy and prognosis, is similar to events of other outcome measures, which allows ranking by summarizing results across all these outcome measures.

Literature search and study selection

The PubMed database was searched. We adopted the literature search strategy described by Botta et al.² In brief, all possible combinations of the following search terms were used for searching RCTs concerning RRMM patients: “multiple myeloma,” “relapse,” “refractory,” “randomized,” “management,” “regimen,” and “therapy.” No specific filters were used during the search. The time range of the search was between the January 1, 2000 and June 30, 2017.

The following predefined eligibility criteria were used for the study selection: 1) the study should be an RCT; 2) the subjects should be RRMM patients; 3) at least two different regimens were compared in the study, except for those comparing different dosing schemes or modes of administrations; 4) data for at least one of the outcome measures were available. Studies that did not match any of the above criteria were excluded.

Two authors (X.W.L. and X.Q.D.) independently performed the literature search and study selection and discussed with the third author (X.M.) to resolve any discrepancies.

Data extraction and statistical analysis

Two authors (X.W.L. and X.Q.D.) independently reviewed the reports. Supplementary materials of the RCTs were included, and the following information was extracted from each study report: name of the first author, year of publication, trial identifications, treatment regimens used for the experimental and control arms, total number of patients, outcome measures investigated, and data for the calculation of effect size for each outcome.

Before NMA, the logarithmic odds ratio (OR) and its standard error were calculated for NRR, and the logarithmic hazard ratio (HR) and its standard error for time-to-event outcomes were original data inputs. Fixed effects Bayesian NMAs were conducted, and forest plots were generated with results shown as the HR and corresponding 95% credible interval (95%CrI). To include all treatments within one network, bortezomib with or without dexamethasone was considered identical and labeled as “bortezomib ± dexamethasone” and thalidomide with or without dexamethasone was considered identical and labeled as “thalidomide ± dexamethasone” as described in van Beurden-Tan et al.¹ The dexamethasone monotherapy was set as the common reference regimen. To rank all regimens, the surface under the cumulative ranking curve (SUCRA) was calculated for each outcome as described in Salanti et al.³ for a given regimen. A larger SUCRA score indicated better efficacy in terms of a specific outcome measure. For the final ranking regarding the overall efficacy, an arithmetic weighted average of SUCRA scores across NRR, PFS, and OS was calculated. A 20%, 35%, and 45% weight was given to the NRR, PFS, and OS, respectively. These weights were given in accordance with the importance of the outcome measures. We considered the OS the most important, PFS as the surrogate of OS the second most important, and NRR that reflects the early efficacy the least important. There was only one exception, oblimersen plus dexamethasone, for which data on PFS and OS were not available, thus an 80% weight was attributed to TTP. A larger weighted average of SUCRAs indicated a higher rank in terms of overall efficacy. The R software version 3.1.2 and the gemtc package were used to perform all the statistical analyses.

Results

Basic information of included RCTs

After literature search and study selection, a total of 29 trial reports published between 2005 and 2017 were considered eligible to be included in the NMA. As a result, 24

independent studies, with a total of 10,853 subjects and 21 different regimens were included in the present study. Compared with the inclusion results by Botta et al,² an additional seven references^{4–10} were included, among which four were newly identified studies^{4,5,9,10} and three were updated study results.^{6–8} The basic information of the included references has been summarized in Table 1.

NMA results

According to the results of NMAs, the combination of daratumumab, lenalidomide, and dexamethasone was the most effective therapy in terms of NRR, TTP, and PFS (NRR: OR = 0.046, 95% CrI = [0.024, 0.085]; TTP: HR = 0.14, 95% CrI = [0.092, 0.2]; PFS: HR = 0.12, 95% CrI = [0.077, 0.18], compared with dexamethasone singlet; Figure 1A–C), and the combination of ixazomib, lenalidomide, and dexamethasone is the most effective one in terms of OS (HR = 0.12, 95%CrI = [0.17, 0.54]; Figure 1D).

Ranking of regimens by SUCRA

As shown in Table 2, the ranking by SUCRA scores for each efficacy outcome was generally consistent with NMA findings. The combination of daratumumab, lenalidomide, and dexamethasone ranked first for NRR (SUCRA = 0.984), TTP (SUCRA = 0.988), and PFS (SUCRA = 0.999). The combination of ixazomib, lenalidomide, and dexamethasone ranked first for OS (SUCRA = 0.972).

In terms of overall efficacy measured by the weighted average of SUCRAs, the combination of daratumumab, lenalidomide, and dexamethasone ranked on top (weighted average = 0.920), followed by the combination of ixazomib, lenalidomide, and dexamethasone (weighted average = 0.907).

Discussion

Regardless of recent progress in management, RRMM is still an incurable disease, which has been attracting substantial research attention. In the past decades, a large number of

Table 1 Basic information of included RCT reports

Authors	Year	Trial Identification	Arm 1	Arm 2	N	Outcome
Richardson et al ¹¹	2005	APEX	BOR	DEX	627	NRR, TTP, OS
Richardson et al ¹²	2007	APEX	BOR	DEX	627	NRR, TTP, OS
Dimopoulos et al ¹³	2007	MM-010	LEN + DEX	DEX	351	NRR, TTP, OS
Orlowski et al ¹⁴	2007	DOXIL-MMY-3001	BOR + pIDOX	BOR + DEX	646	NRR, TTP, PFS, OS
Weber et al ¹⁵	2007	MM-009	LEN + DEX	DEX	353	NRR, TTP, OS
Chanan-Khan et al ¹⁶	2009	GMV302	OBL + DEX	DEX	224	NRR, TTP
Dimopoulos et al ¹⁷	2009	MM-009 & MM-010	LEN + DEX	DEX	704	PFS, OS
Garderet et al ¹⁸	2012	MMVAR/IFM 2005-04	BOR + THA + DEX	THA + DEX	244	NRR, TTP, PFS, OS
Hjorth et al ¹⁹	2012	NCT00602511	THA + DEX	BOR + DEX	131	NRR, PFS, OS
Kropff et al ²⁰	2012	OPTIMUM	THA	DEX	499	NRR, TTP, PFS, OS
Dimopoulos et al ²¹	2013	VANTAGE 088	VOR + BOR	BOR	635	NRR, TTP, PFS, OS
San-Miguel et al ⁴	2013	MM-003	POM + DEX	DEX	455	NRR, TTP, PFS, OS
White et al ²²	2013	AMBER	BEV + BOR	BOR	102	NRR, PFS, OS
Morgan et al ⁶	2014	MM-003	POM + DEX	DEX	455	OS
Richardson et al ⁵	2014	MM-002	POM + DEX	POM	221	NRR, PFS, OS
San-Miguel et al ²³	2014	PANORAMA I	PAN + BOR + DEX	BOR + DEX	768	NRR, TTP, PFS, OS
Lonial et al ²⁴	2015	ELOQUENT-2	ELO + LEN + DEX	LEN + DEX	646	NRR, PFS
Orlowski et al ²⁵	2015	NCT00401843	SIL + BOR	BOR	268	NRR, TTP, PFS, OS
Stewart et al ²⁶	2015	ASPIRE	CAR + LEN + DEX	LEN + DEX	792	NRR, PFS, OS
Dimopoulos et al ²⁷	2016	POLLUX	DAR + LEN + DEX	LEN + DEX	557	NRR, TTP, PFS, OS
Dimopoulos et al ²⁸	2016	ENDEAVOR	CAR + DEX	BOR + DEX	929	NRR, PFS, OS
Jakubowiak et al ²⁹	2016	NCT01478048	ELO + BOR + DEX	BOR + DEX	152	NRR, PFS, OS
Moreau et al ³⁰	2016	TOURMALINE-MM1	IXA + LEN + DEX	LEN + DEX	722	NRR, TTP, PFS
Orlowski et al ³¹	2016	DOXIL-MMY-3001	BOR + pIDOX	BOR + DEX	646	OS
Palumbo et al ³²	2016	CASTOR	DAR + BOR + DEX	BOR + DEX	474	NRR, TTP, PFS, OS
San-Miguel et al ⁷	2016	PANORAMA I	PAN + BOR + DEX	BOR + DEX	768	OS
Dimopoulos et al ⁸	2017	ELOQUENT-2	ELO + LEN + DEX	LEN + DEX	646	PFS, OS
Hou et al ¹⁰	2017	NCT01564537	IXA + LEN + DEX	LEN + DEX	115	NRR, TTP, PFS, OS
Hajek et al ⁹	2017	FOCUS	CAR	DEX	315	NRR, PFS, OS

Abbreviations: BOR, bortezomib; BEV, bevacizumab; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; pIDOX, Pegylated liposomal doxorubicin; ELO, elotumumab; IXA, ixazomib; LEN, lenalidomide; OBL, oblimersen; POM, pomalidomide; SIL, siltuximab; THA, thalidomide; NRR, non-response rate; PAN, panobinostat; PFS, progression-free survival; TTP, time to progression; OS, overall survival; N, number of patients; VOR, vorinostat.

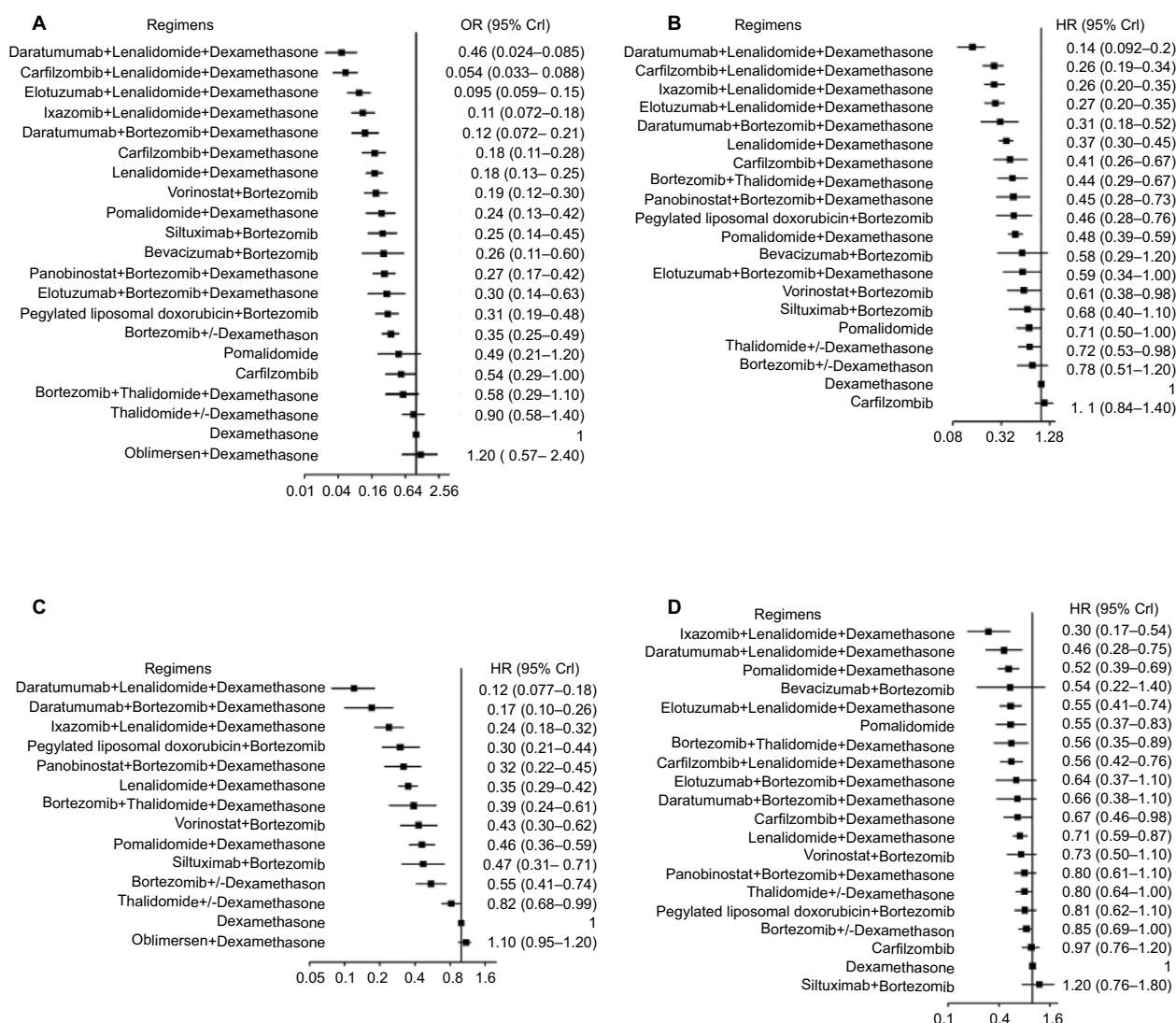


Figure 1 Forest plots presenting results of network meta-analysis: (A) nonresponse rate, (B) progression-free survival, (C) time to progression, (D) overall survival. **Abbreviations:** OR, odds ratio; CrI, credible interval; HR, hazard ratio.

RCTs concerning RRMM treatment were published, in which dozens of novel therapeutic regimens were tested and examined. Efforts were made to quantitatively summarize the evidence from RCTs by performing NMA, in order to provide useful and important information for clinical decision-making at minimal cost. However, flawed analyses may result in misleading conclusions. On the other hand, updates of NMAs on a timely basis are the key to keep the evidence “alive.” The present study included the most recently published trials and updates of previous trial reports, thoroughly investigated the efficacy profiles of 21 treatment options, and avoided certain limitations of previous NMAs mentioned above.

According to our results, the combination of daratumumab, lenalidomide, and dexamethasone was most effective in terms of NRR, TTP, and PFS. However, in terms of OS, it was less effective compared with the combination of ixazomib, lenalidomide, and dexamethasone. Ranking by overall efficacy showed that the daratumumab, lenalidomide, and dexamethasone triplet regimen had better performance than other regimens. Interestingly, we noted that the 21 regimens investigated in this NMA can be categorized into three subgroups based on the weighted average of SUCRA scores. The first subgroup includes four regimens (19.0%, weighted average from ~0.8 to ~0.9), which are the most

Table 2 Included regimens, SUCRAs, weighted averages of SUCRAs across NRR, TTP, and OS, and ranks in terms of overall efficacy

Regimens	NRR	TTP	PFS	OS	Weighted average	Rank
Daratumumab + lenalidomide + dexamethasone	0.984	0.988	0.999	0.829	0.920	1
Ixazomib + lenalidomide + dexamethasone	0.828	0.828	0.869	0.972	0.907	2
Carfilzomib + lenalidomide + dexamethasone	0.964	NA	0.887	0.697	0.817	3
Elotuzumab + lenalidomide + dexamethasone	0.873	NA	0.855	0.72	0.798	4
Daratumumab + bortezomib + dexamethasone	0.813	0.927	0.812	0.539	0.689	5
Pomalidomide + dexamethasone	0.539	0.393	0.512	0.771	0.634	6
Carfilzomib + dexamethasone	0.683	NA	0.638	0.527	0.597	7
Lenalidomide + dexamethasone	0.66	0.609	0.685	0.447	0.572	8
Bortezomib + thalidomide + dexamethasone	0.202	0.531	0.581	0.689	0.554	9
Bevacizumab + bortezomib	0.5	NA	0.38	0.656	0.528	10
Elotuzumab + bortezomib + dexamethasone	0.429	NA	0.358	0.564	0.465	11
Pomalidomide monotherapy	0.252	NA	0.25	0.698	0.452	12
Vorinostat + bortezomib	0.661	0.446	0.342	0.433	0.447	13
Panobinostat + bortezomib + dexamethasone	0.472	0.678	0.566	0.327	0.43965	14
Pegylated liposomal doxorubicin + bortezomib	0.406	0.715	0.55	0.305	0.41095	15
Thalidomide ± dexamethasone	0.083	0.153	0.221	0.325	0.2402	16
Bortezomib ± dexamethasone	0.329	0.263	0.149	0.235	0.2237	17
Siltuximab + bortezomib	0.511	0.391	0.259	0.048	0.21445	18
Carfilzomib monotherapy	0.214	NA	0.029	0.132	0.11235	19
Dexamethasone monotherapy	0.057	0.068	0.059	0.089	0.0721	20
Oblimersen + dexamethasone*	0.041	0.011	NA	NA	0.017	21

Notes: A 20%, 35%, and 45% weight was given to the NRR, PFS, and OS, respectively. *Since data on PFS and OS were not available, a 20% and 80% weight was assigned to NRR and TTP, respectively.

Abbreviations: NA, not available; NRR, non-response rate; TTP, time-to-progression; PFS, progression-free survival; OS, overall survival.

effective ones, with lenalidomide and dexamethasone as the backbone plus one of the four latest agents (daratumumab, ixazomib, carfilzomib, or elotumumab). The second subgroup includes 11 regimens (52.4%, weighted average from ~0.4 to ~0.7), which show moderate efficacy in RRMM patients and are mostly doublet or triplet regimens. The third subgroup includes six regimens (28.6%, weighted average from 0.0 to 0.25), which are mostly singlet or doublet regimens having limited efficacy.

An important advantage of NMA over traditional meta-analysis is the possibility of ranking multiple treatment options. The SUCRA score, derived from the probability that a given treatment has a certain rank and calculated from the posterior distributions of all treatments, is widely used for ranking treatments in Bayesian NMAs. In this study, we applied a weighted averaging strategy to rank the regimens for overall efficacy. We assigned weights to different outcome measures in accordance with their importance. The OS is the “gold standard” outcome measure for the evaluation of long-term anticancer efficacy, the PFS and TTP are widely acknowledged surrogates of OS, and the treatment response associated with early efficacy may differ from long-term outcomes. Therefore, we gave a 20%, 35%, and 45% weight to NRR, PFS/TTP, and

OS, respectively. We did not take safety into account, because to date no adequate data were available to include all treatment options in one network for any single adverse event outcome. A systematic review less quantitatively intense may be a good choice for further investigation on safety profiles. We do not recommend any ranking based on a combined quantitative analysis of efficacy and safety, because they are two facets distinct from one another, and it is very difficult to assign a rational and appropriate weight to each outcome.

The present study, similar to its preceding works, also has some limitations. First, although the relative importance of different outcome measures was considered, the appropriateness of the arbitrary assignment of weights needs further verification. Besides, it should acknowledge the limitations of the NMA fully when comparing benefits from the experimental treatments in patient populations that differ in previous treatments, cytogenetic risks, subsequent stem-cell transplantation, maintenance therapy, and so on. Although it could be possible to make adjustment by using approaches such as network meta-regression, the immaturity of methodology, limited number of included trials and frequent missingness in certain study-level variables make it difficult and less reliable.

Conclusion

In conclusion, the combination of daratumumab, lenalidomide, and dexamethasone may currently be the most effective regimen in the population of RRMM patients. Triplet regimens containing daratumumab, ixazomib, carfilzomib, or elotumumab plus lenalidomide and dexamethasone can be recommended as the first-line therapies for RRMM patients.

Disclosure

The authors report no conflicts of interest in this work.

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