MultipleMyelomaHub

Relapsed/refractory patients

Literature and network meta-analysis to assess efficacy of RRMM treatment options

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For patients with relapsed and refractory Multiple Myeloma (RRMM), there are a wide range of treatment options currently available. Whilst this is positive for patients, it has complicated the decision making process, putting pressure on doctors to select the best therapy at a given point in time, whilst balancing other factors such as patient health and age, prior treatment regimens and co-morbidities. In addition, data directly comparing the different regimens is lacking. In a study led by Chrissy van Beurden-Tan and Professor Pieter Sonneveld from the Erasmus MC Cancer Institute, Rotterdam, The Netherlands, and published in the Journal of Clinical Oncology in April 2017, treatment options for patients with RRMM were compared directly using a systematic literature review that included network meta-analyses (NMA).

Key Highlights:

- Literature search carried out between January 1999 and March 2016, to identify relevant phase III randomized controlled trials (RCTs) treating RRMM patients
- Databases searched: Embase, MEDLINE, MEDLINE In-Process, Cochrane Central Register of Controlled Clinical Trials, and www.ClinicalTrials.gov, as well as trials from data presented at ASCO 2016 and EHA 2016
- 18 treatment options identified across 17 trials (see table below for abbreviations)
- In order to include all trials within one framework, several assumptions were made: bort alone was the same as BortDex, Thal alone was the same as ThalDex, TTP could be used in the place of PFS if HRs or 95% CIs of PFS were missing, there was no difference due to administration methods, and dose differences were disregarded and the data pooled

Results:

- DaraLenDex was the most effective treatment for RRMM in 99% of simulations
- HR DaraLenDex *vs.* Dex = 0.13 (95% CI, 0.09 to 0.19); indicating 87% reduced risk of progression or death
- CarLenDex, EloLenDex, DaraBorDex, and IxaLenDex ranked joint second in terms of efficacy
- Treatments significantly better than Dex = 14/15; HR *vs.* Dex ranged from 0.13-1.08; only ObIDex ranked lower than Dex alone with HR = 1.08
- 11 treatments reduced the risk of death by >50% *vs.* Dex
- HRs *vs.* BorDex ranged from 0.19-1.57; treatments significantly better than BorDex = 12/15
- HRs *vs.* LenDex ranged from 0.37-3.0; treatments significantly better than LenDex = 4/15 (DaraLenDex, Car-LenDex, EloLenDex, and IxaLenDex)

- No Bor-backbone regimens showed better efficacy than LenDex, apart from DaraBorDex, although HR did differ significantly from LenDex, HR = 0.73; 95% CrI, 0.48-1.15
- The risk reduction of progression or death *vs.* BorDex: ranged from VorinoBor = 23% to DaraLenDex = 81%
- The risk reduction of progression or death *vs.* LenDex: ranged from IxaLenDex = 26% to DaraLenDex = 63%

In conclusion, this meta-analysis identified the triplet regimen of DaraLenDex as the most effective treatment for RRMM patients, with an 87% reduction in the risk of progression or death when compared to other common regimens. The regimens rated second and third most effective were also triplet combinations. This is not surprising in light of the positive data coming from daratumumab phase III trials, and the mounting evidence in favor of triplet regimens in general.

Whilst this type of analysis is useful to help make sense of the myriad options currently available, careful consideration must be taken when assimilating the data, and treatment options still considered on an individual basis.

Indeed, some aspects of this study were questioned in a Correspondence written by Xavier Armoiry and colleagues from Warwick University Medical School, UK. They expressed reservations regarding the validity of the HR estimates for LenDex *vs.* BorDex, using the assumption that Bor monotherapy is the same as BorDex. Although no studies have compared Bor with BorDex directly, two observational studies did compare the regimens. A meta-analysis of these two studies gave a HR of 0.65, which is in disagreement with the assumption of equivalency between Bor and BorDex. Using the same argument that comparative studies should have been included, and not just RCTs, a HR of 0.99 was calculated for BorDex *vs.* LenDex, in contrast to the calculation of HR = 0.52 by van Beurden-Tan *et al.* Armoiry and colleagues did point out the limitations of their suggestion as well, but argue that it is more robust than the exclusion of non-RCT data and the assumptions made. In addition, they suggested that the authors could have included other data, such as that published by companies as part of their submissions to NICE, and suggested this could have helped to avoid the use of HR to replace TTP, in the absence of PFS.

In a reply to this communication, van Beurden-Tan *et al.* thanked the authors for their consideration of the study, but argued that a meta-analysis of just two studies had larger limitations, especially when the data from these studies was not statistically significant. Similarly, they argued that using non-RCT data has major consequences, as it is difficult to ensure compatibility and avoid selection bias. They purported that limiting data to only phase III trials avoids this. They did concede however, that their assumption of equivalency between Bor *vs.* BorDex does have limitations, but found that using a HR of 0.99 did not alter the overall conclusions of their study in terms of the ranking of different therapies; it was found to only effect the lower ranking of Dara plus BorDex (a change from HR = 0.27 to 0.22).

This conversation illustrates the degree of commitment that exists in finding the best answers for treatment options, and such exchanges are essential to drive research forward in order to find the best way of evaluating data, and importantly deciding on treatment regimens to put into practice. Clinicians can use such a meta-analysis as an important reference, while at the same time considering their own anecdotal evidence and evaluating patients on an individual basis according to their individual characteristics and clinical assessments. However, if the conclusion of this study is true, then the availability and cost of daratumumab are issues that need to be addressed, so that the most effective option is available to all.

Treatment options for RRMM identified from the literature search:

	Treatment	Abbreviation
1	Dexamethasone	Dex
2	Oblimersen plus dexamethasone	OblDex
3	Thalidomide	Thal
4	Thalidomide plus Dexamethasone	ThalDex
5	Bortezomib	Bor
6	Bortezomib plus Dexamethasone	BorDex
7	Lenalidomide plus Dexamethasone	LenDex
8	Pegylated Liposomal Doxorubicin plus Bortezomib	PegDoxBor
9	Bortezomib, thalidomide, and dexamethasone	BorThalDex
10	Vorinostat plus Bortezomib	VorinoBor
11	Panobinostat, Bortezomib, and Dexamethasone	PanoBorDex
12	Carfilzomib, Lenalidomide, and Dexamethasone	CarLenDex
13	Pomalidomide plus Dexamethasone	PomDex
14	Elotuzumab, lenalidomide, and Dexamethasone	EloLenDex

15	Carfilzomib plus Dexamethasone	CarDex
16	Ixazomib, Lenalidomide, and Dexamethasone	IxaLenDex
17	Daratumumab, Lenalidomide, and Dexamethasone	DaraLenDex
18	Daratumumab, Bortezomib, and Dexamethasone	DaraBorDex

Abstract

Purpose: Since 2000, many new treatment options have become available for relapsed and/or refractory multiple myeloma (R/R MM) after a long period in which dexamethasone and melphalan had been the standard treatment. Direct comparisons of these novel treatments, however, are lacking. This makes it extremely difficult to evaluate the relative added value of each new treatment. Our aim was to synthesize all efficacy evidence, enabling a comparison of all current treatments for R/R MM. Methods We performed a systematic literature review to identify all publicly available phase III randomized controlled trial evidence. We searched Embase, MEDLINE, MEDLINE In-Process, Cochrane Central Register of Controlled Clinical Trials, and the Web site www.ClinicalTrials.gov . In addition, two trials presented at two international hematology congresses (ie, ASCO 2016 and European Hematology Association 2016) were added to include the most recent evidence. In total, 17 randomized controlled trials were identified, including 18 treatment options. The evidence was synthesized using a conventional network meta-analysis. To include all treatments within one network, two treatment options were combined: (1) bortezomib monotherapy and bortezomib plus dexamethasone, and (2) thalidomide monotherapy and thalidomide plus dexamethasone. Results: The combination of daratumumab, lenalidomide, and dexamethasone was identified as the best treatment. It was most favorable in terms of (1) hazard ratio for progression-free survival (0.13; 95% credible interval, 0.09 to 0.19), and (2) probability of being best (99% of the simulations). This treatment combination reduced the risk of progression or death by 87% versus dexamethasone, 81% versus bortezomib plus dexamethasone, and 63% versus lenalidomide plus dexamethasone. Conclusion: Our network meta-analysis provides a complete overview of the relative efficacy of all available treatments for R/R MM. Until additional data from randomized studies are available, on the basis of this analysis, the combination of daratumumab, lenalidomide, and dexamethasone seems to be the best treatment option.

References

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