Correspondence

Letter: Quest for the Best in Relapsed/Refractory Multiple Myeloma: A Mis-placed ENDEAVOR

Dear Dr. Shader:

Results from the Maiese et al[1] network meta-analysis (NMA) should not be used to inform treatment decisions because the analysis was significantly flawed. First, the trials included in the NMA violated the similarity and consistency assumptions for NMAs, leading to biased treatment effects.[2] Second, only a small number of trials contributed to the NMA, preventing adjustment for differences in patient characteristics across dis-similarly designed trials. Finally, the most important end points to clinicians and patients—overall survival (OS), quality of life (QOL), and safety—were not considered in the analysis.

When published evidence is inadequate to enable a valid NMA, authors must rely on assumptions, which can introduce significant bias and confound the interpretation of results. Maiese et al[1] encountered such a situation, and some specifics on the questionable decisions/assumptions that they made are as follows.

- Heterogeneity in therapy duration among trials included in the NMA was not addressed. In CASTOR (Phase 3 Study Comparing DVd Versus Vd in Subjects with RRMM),[3] bortezomib plus dexamethasone (Vd) duration was capped at 6 months. In ENDEAVOR (Randomized, Open Label, Phase 3 Study of Carfilzomib Plus Dexamethasone Vs Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma),[4] Vd was used to treat-to-progression, and nearly 50% received Vd beyond 6 months. In their appraisal, the National Institute for Health and Care Excellence committee concluded that capping treatment duration instead of treat-to-progression would reduce Vd efficacy.[5] In the case of carfilzomib plus lenalidomide plus dexamethasone (KRd), carfilzomib duration was capped at 18 cycles. All other Rd triplet regimens in the NMA were continued until progression, leading to comparisons of trials that were dis-similar in design, specifically duration of therapy (a key driver of outcomes in multiple myeloma). Trial data show "treatment effect for the period prior to stopping carfilzomib was higher than for the overall study."[6]
- OS or QOL data were not considered. QOL data have not been reported consistently from relapsed/refractory multiple myeloma trials, and OS results are inconclusive for most trials. Among the comparators in the Maiese et al[1] NMA, only carfilzomib regimens demonstrated superiority over both Rd and Vd on OS and QOL in randomized Phase III trials.
- Relative efficacy (progression-free survival [PFS]) of the triplet regimen daratumumab plus Vd (DVd) was compared with a doublet regimen of carfilzomib plus dexamethasone without considering the incremental toxicity of the former. The added toxicity of the triplet regimen may be borne out as the difference in benefit duration; the doublet regimen of carfilzomib plus dexamethasone achieved a median PFS of 18.7 months and the triplet combination DVd achieved a median PFS of 16.7 months.[3]
- Heterogeneity in the inclusion/exclusion criteria across trials led to differences in the baseline characteristics of the study populations, which is evident from differences in the median PFS for Rd across trials. The analysis could not adjust for prognostic factors (age, Eastern Cooperative Oncology Group performance status, International Staging System, cytogenetic risk, and number and type of previous therapies) because the network was limited to a small number of studies with single pair-wise comparisons. An attempt at using meta-regressions to control for heterogeneity produced models that did not converge, thereby eliminating any possibility of reducing bias in relative treatment effects.

The highlighted flaws lead to biased results, and any sensitivity analysis is prone to these limitations. Clinicians must consider head-to-head trial data, patient factors, and goals to arrive at treatment decisions.

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REFERENCES

1. Maiese EM, Ainsworth C, Le Moine JG, et al. Comparative efficacy of treatments for previously treated multiple myeloma: a systematic literature review and network meta-analysis. *Clin Ther*. 2018;40:480—494. e23.
2. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR task force on indirect treatment comparisons good research practices: part 2. *Value Health*. 2011;14:429—437.
3. Spencer A, Hungria VT, Mateos MV, et al. Daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): updated efficacy and safety analysis of CASTOR. https://ash.confex.com/ash/2017/webprogram/Paper104182.html. Accessed 19 March 2018.
4. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18:1327—1337.
5. National Institute for Health and Care Excellence. Final appraisal determination: carfilzomib for previously treated multiple myeloma. https://www.nice.org.uk/guidance/ta457/documents/final-appraisal-determination-document. Accessed 19 March 2018.
6. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2018;36:728—734.

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