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Meta-analysis to Evaluate High-Dose Therapy Followed by Stem Cell Transplant in Patients With Multiple Myeloma

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To the Editor Dhakal et al¹ used conventional meta-analysis techniques to address an important question regarding the efficacy of high-dose therapy followed by autologous stem cell transplant (HDT/ASCT) vs standard care in patients with multiple myeloma. The primary outcome was progression-free survival (PFS), with overall survival (OS) as a secondary end point. Four comparative randomized clinical trials were included in this meta-analysis. For each study, the hazard ratio (HR) was used to quantify the treatment effect for both PFS and OS. Because significant heterogeneity in HR was observed across studies for both PFS and OS, a random-effects model was used to obtain a pooled HR for the overall treatment effect from HDT/ASCT. Specifically, those underlying HRs from 4 study populations were likely different and we assume that these 4 separate HRs were a random sample from a hypothetical superpopulation characterized by log-normal distribution. This resulted in the combined HR of 0.55 for PFS (95% CI, 0.41-0.74; $P < .001$) and of 0.76 for OS (95% CI, 0.42-1.36; $P = .20$) in favor of HDT/ASCT.

There are limitations when taking this approach to evaluate overall treatment effect of HDT/ASCT. First, HR is not easy to interpret clinically.² Second, it is well known that when the number of studies is small (eg, $n = 4$), the conventional random-effects model can produce confidence intervals that are inappropriately narrow and fail to reflect the true uncertainty in the data.^{3,4} Third, the assumed log-normal distribution of the true study-level HRs from the aforementioned superpopulation may be misspecified and lead to incorrect conclusions. Fourth, an issue for a random-effects approach is that the assumption of selected studies being a random sample from a superpopulation of studies is generally not well defined or easily understood.⁵ It is not clear whether a future study population of interest would be a member of this same superpopulation. Even if the future study is a member of the superpopulation, the true treatment effect in that population may differ substantially from the estimate obtained from the random-effects model because the latter is merely an average across the spectrum of all theoretically possible treatment effects.

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A fundamental principle in conducting any comparative study is to first define the patient population and intervention of interest and then to collect data for making inference about the treatment effect for that population. One needs to follow the same principle for conducting meta-analysis. It is not informative to rely on a single average estimate of the treatment effect, especially when the treatment effects may vary substantially across different target populations.⁵

References

1. Dhakal B, Szabo A, Chhabra S, et al. Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis. *JAMA Oncol.* 2018;4(3):343–350. doi:10.1001/jamaoncol.2017.4600 [PubMed: 29302684]
2. Pak K, Uno H, Kim DH, et al. Interpretability of cancer clinical trial results using restricted mean survival time as an alternative to the hazard ratio. *JAMA Oncol.* 2017;3(12):1692–1696. doi: 10.1001/jamaoncol.2017.2797 [PubMed: 28975263]
3. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. *Stat Med.* 2001;20(6):825–840. doi:10.1002/sim.650 [PubMed: 11252006]
4. Henmi M, Copas JB. Confidence intervals for random effects meta-analysis and robustness to publication bias. *Stat Med.* 2010;29(29):2969–2983. doi:10.1002/sim.4029 [PubMed: 20963748]
5. Hasegawa T, Claggett B, Tian L, Solomon SD, Pfeffer MA, Wei LJ. the myth of making inferences for an overall treatment efficacy with data from multiple comparative studies via meta-analysis. *Stat Biosci.* 2017;900:284–297. doi:10.1007/s12561-016-9179-3