Comment on Jiang G. et al.: Efficacy and safety between temozolomide alone and temozolomide-based double therapy for malignant melanoma: a meta-analysis

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Dear Editor,

We read with great interest the recent paper by Jiang G. et al., “Efficacy and safety between temozolomide alone and temozolomide-based double therapy for malignant melanoma: a meta-analysis,” published online in *Tumor Biology* [1]. The investigators performed a meta-analysis of five randomized controlled trials to compare the clinical efficacy and safety of temozolomide (TMZ) alone and TMZ-based combination drug therapy in patients with melanoma. It is a very interesting study. Nevertheless, we have several queries which we would like to communicate with the investigators.

1. It is not appropriate that the summary risk ratio (RR) estimate with corresponding 95 % CIs was derived by using the method of Mantel–Haenszel (M–H) with the assumptions of a random-effects model (Figure 6). However, studies should be combined by using the DerSimonian and Laird random-effects model.
2. The meta-analysis results of the hematological toxicities suggested that the heterogeneity (I^2) was found to be more than 75 %. This showed significantly higher variations between studies, so they are not comparable, which could potentially bias the results of this study. Moreover, I^2 values above 90 % are very rare in any meta-analysis. We are eager to know the investigators’ opinion about this case.

3. Inclusion criteria were not adequate in the meta-analysis. We suggest that all the three included RCTs that were performed exclusively in adults (≥ 18 years old) except pregnant and lactating female patients should be included.
4. In the results part, the funnel plot was used to estimate publication bias, and the symmetric inverse funnel distribution was obtained. However, the funnel plot was not present, and the number of randomized controlled trials was only 5. As we know, a funnel plot should be inspected visually to assess for publication bias in meta-analyses with sufficient number of studies (more than nine). Meanwhile, it is not sufficient that publication bias was only assessed by visual examination of the funnel plot. In our opinion, funnel plot symmetry should be further assessed by statistical tests (e.g., Egger’s linear regression test or Begg’s rank correlation test).
5. The investigators did not follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). As a minor suggestion, adding a PRISMA checklist as a summary might make this manuscript better.

In conclusion, the results of the meta-analysis by Jiang G. et al. should be interpreted with caution. To reach a definitive conclusion, further studies based on more carefully and scientifically designed RCTs with large sample sizes are still needed to compare the clinical efficacy and safety of TMZ alone and TMZ-based combination drug therapy in patients with melanoma. We believe that our remarks will contribute to a more accurate elaboration of the results presented by Jiang G. et al.

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