Table 1. Clinical characteristics and response to immunosuppression and growth factors treatment.

Pt/Diagnosis	Previous Treatment	Initial Hb/transf	Final Hb/transf	Changes Hb/transf 12 week-18week-24week	Response
1/ARS	r-hu-Epo	82/No	81/No		No
2/ARS	Darbepoetin	85/Yes	87/Yes		No
3/ARS	Darbepoetin	92/Yes	96/No	95/Y-83/N-96/N	Major
4/RCMD-S	r-hu-Epo	94/Yes	100/Yes		No
5/RCMD-S	No Epo > 300 u/L	81/No	109/No	99/N-96/N-109/N	Major
6/RCMD-S	No Epo > 300 u/L	87/Yes	-	-	Drop-out
7/ARS	Darbepoetin	77/Yes	78/Yes	-	No
8/ARS	Darbepoetin	71/Yes (6 u*)	82/Yes (2u)	83/Y(9u)-82/Y(2u)-82/Y(2u)	Minor (<50% transfusions)
9/ARS	Darbepoetin	86/Yes	97/No	89/Y-96/N-97/N	Major
10/RCMD-S	Darbepoetin	85/No	101/No	84/N-101/N-101/N	Minor

*Units per month. Pt: patient. ARS: refractory anemia with ring sideroblasts. RCMD-S: refractory cytopenia and multilinial dysplasia with ring sideroblasts. R-hu-Epo recombinant human erythropoietin. Transf: transfusions, Y: Yes, N:No. Hb in g/L.

This approach is easy to manage and well-tolerated, and does not require hospital admission.

In summary, using the scheme of oral immunosuppresion and growth factors, in 3 out of the 9 LR-MDS patients transfusions were no longer required. Obviously, larger studies should be carried out to confirm and validate this scheme of treatment. Immunosuppression and growth factors could be an alternative to new drugs that have appeared recently.

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Key words: myelodysplastic syndrome, erythropoietin, immunosuppression, mycophenolate.

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Decitabine *versus* 5-azacitidine for the treatment of myelodysplastic syndrome: adjusted indirect meta-analysis

We read with great interest the systematic review and meta-analysis by Gurion *et al.* assessing the efficacy of hypomethylating agents (HMA) versus supportive care for the treatment of patients with myelodysplastic syndromes (MDS).[1] The meta-analysis included 4 randomized controlled trials (RCT). As the authors noted, we also performed a meta-analysis/systematic review on the same topic that included the same RCTs.[2,3] For the benefit of the medical community, it is important to see the reproducibility achieved by two groups working independently. Our

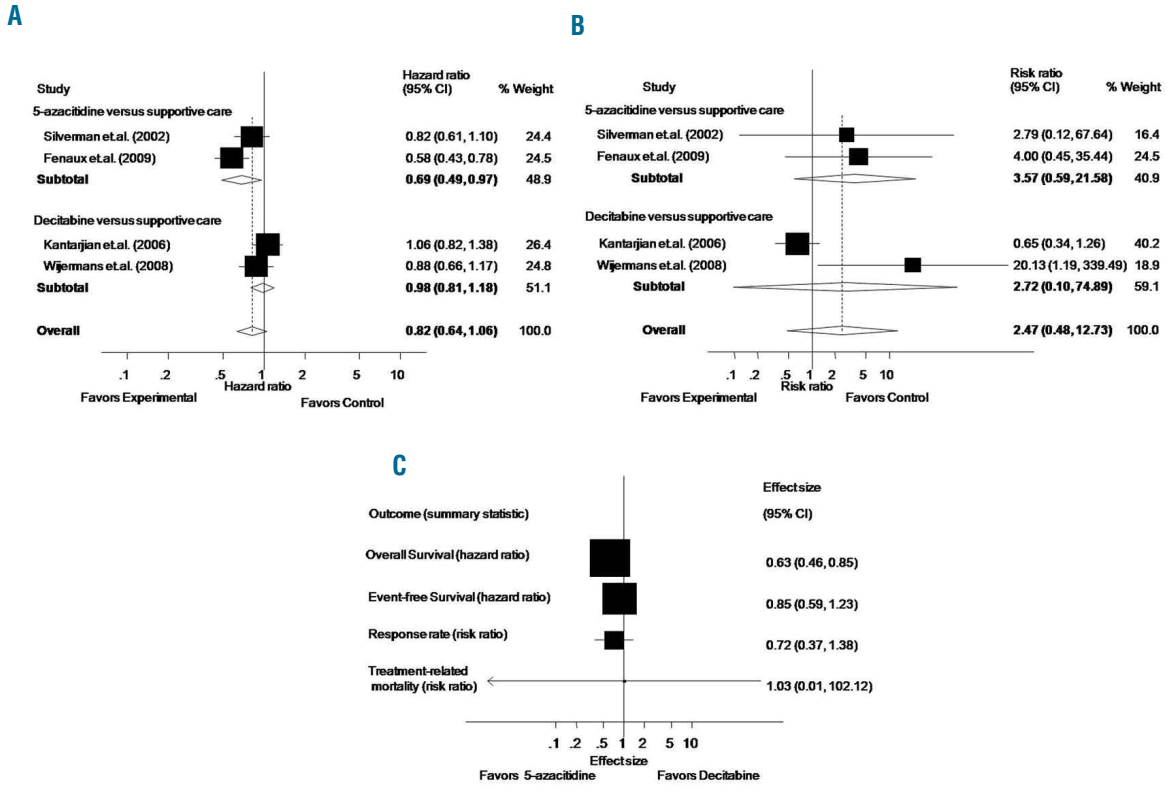

Figure 1. Meta-analysis for the outcome of overall survival (A) and treatment-related mortality (B) of 952 patients enrolled in 4 randomized controlled trials. Adjusted indirect meta-analysis of randomized controlled trials on the efficacy of hypo-methylating agents for the treatment of myelodysplastic syndromes (C). The pooled summary effect estimate (hazard ratio/risk ratio) for each study/outcome is indicated by black rectangles, with the lines representing 95% confidence intervals (CIs). The vertical line indicates no difference between two treatments.

meta-analysis conclusions differed slightly and contained additional elements, which in our opinion, further strengthens the report by Gurion and colleagues.[1]

First, Gurion *et al.*[1] did not report survival data from the study by Kantarjian *et al.*[4] We were able to extract survival data from that study using the Parmar method.[5] Second, for the study of Silverman *et al.*,[6] we calculated a hazard ratio of 0.82 and corresponding 95% CI of 0.61-1.10, a statistically non-significant difference, while Gurion *et al.*[1] reported a statistically significant difference between 5-azacitidine and supportive care with a hazard ratio of 0.52 along with 95% CI of 0.32-0.86. We believe our data are closer to the original estimates since Silverman *et al.*[6] also reported a statistically non-significant difference in median survival between the 5-azacitidine and supportive care for the intention-to-treat population (*P*=0.10). The inclusion of survival data from the study by Kantarjian *et al.*,[4] as well as corrected hazard ratio for survival by Silverman *et al.*[6] impacts the results of the meta-analysis. As shown in Figure 1A, pooled results from 4 RCTs enrolling 952 patients show no difference in overall survival for the comparison of HMA versus supportive care (hazard ratio 0.82, 95% CI 0.64-1.06; *P*=0.124) while Gurion *et al.* report overall survival benefit with HMA (hazard ratio 0.71, 95% CI 95% CI 0.58-0.87).[1] It is important to note, however, that for the comparison of 5-azacitidine *versus* supportive care the survival benefit still holds (hazard ratio 0.62, 95% CI 0.48-0.78; *P*=0.030). On the other hand, a survival benefit was not seen for the decitabine *versus* supportive care. The pooled hazard ratio for overall survival comparing decitabine versus supportive care from 2 trials, instead of one trial reported by Gurion *et al.*,[1] enrolling 403 patients, instead of 233,[4,7] is 0.98 and the corresponding 95% CI is 0.81-1.18 (*P*=0.815).

We also obtained a somewhat different estimate for treatment-related mortality. Gurion *et al.*[1] pooled 3 trials and the results showed that HMA are associated with a statistically significant risk for treatment-related mortality (risk ratio 7.27, 95% CI 1.67-31.64). As shown in Figure 1B, when all 4 trials are included in the meta-analysis, the risk ratio for treatment-related mortality (4 RCTs, 952 patients) is 2.47 with 95% CI 0.48-12.73 (*P*=0.281) indicating a statistically non-significant difference with HMA versus supportive care.[8-10]

Finally, we performed an adjusted indirect meta-analysis to assess the efficacy of 5-azacitidine compared to decitabine using the methods of Bucher,[8] Lumley[10] and Glenny *et al.*[9] According to this method, an unbiased indirect comparison of interventions of 5-azacitidine versus decitabine can be obtained by adjusting the results of their direct comparisons with a common intervention of supportive care, representing the preferred approach in the absence of a prospective randomized head-to-head study. As shown in Figure 1C, an indirect comparison of 5-azacitidine versus decitabine showed a statistically significant benefit for the outcome of overall survival with 5-azacitidine. The hazard ration for overall survival is 0.63 (95% CI 0.46-0.85; *P*=0.003). However, there was no difference between 5-azacitidine and decitabine for time to AML transformation or death (HR 0.85; 95% CI 0.59-1.23; *P*=0.406), response rate (risk ratio 0.716; 95% CI 0.372-1.375; *P*=0.315, using the number of non-responders) or

treatment related mortality (risk ratio 1.026; 95% CI 0.01-102.118; *P*=0.991).

The results presented here are an important addition to and complement the systematic review by Gurion *et al.*[1] They provide greater precision to the existing results and the supplemental analyses, which in turn will be helpful in making informed decisions on the choice of an optimal HMA for the treatment of MDS in the absence of randomized comparisons.

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Meta-analysis on hypomethylating agents in myelodysplastic syndromes

The addition of hypomethylating agents into the armatorium against myelodysplastic syndromes (MDS) is commonly accepted as a promising new therapeutic option in this otherwise frustrating field. However, due to methodological aspects, it is still the subject of debate whether these compounds prolong survival when compared to other treatment modalities in this population.

Meta-analysis is an important tool for summarizing scientific data from different sources and may be of great help in clinical decision making, guideline development and the conception of new trials. In order to obtain meaningful and valid results from such investigations, it is of utmost importance that a high level of unbiased analytical accuracy is ensured.

We have read the recent work of Gurion *et al.*[1] with great interest and would like to express our concerns with respect to the applied methodology which, in our eyes, does not support the conclusion given in the title.

Using the sources cited in the above publication, we were unable to reconstruct the meta-analysis for overall survival (OS). For the trial of Silverman and co-workers[2] we estimated the hazard ratio (HR) to be 0.80 (95% confidence interval 0.57-1.12) for the intention-to-treat (ITT)-analysis and not 0.52 (0.32-0.86) as given by Gurion *et al.* Our result is in line with the original publication which states that median survival had a *P* value of 0.10. Using our estimate, the final result of the meta-analysis for OS is 0.74 (0.57-0.96) instead of 0.66 (0.55-0.80).

For the interpretation of these calculations, the cited study of Kantarjian *et al.* must be considered[3] where it reads: "The ITT-analysis […] indicates that median survival was not significantly different […] *P*=0.636." While there is insufficient information to calculate a HR, it seems plausible that the addition of this trial may change the result of the meta-analysis to a non-significant result. In our opinion, the problem of missing data is a shortcoming of the presented OS meta-analysis and we regret that this important point has not been discussed by the authors.

Instead, in the Discussion section, the authors mention only a few limitations of the data. This again might be a consequence of the fact that the quality assessment in this analysis was limited to randomization (sequence generation, allocation concealment) and blinding. As a crossover between trial arms after randomization as in the Silverman study may be an important source of bias, this is especially relevant. More generally, the completeness of the outcome data was not discussed. In addition, another important source of bias called *selective outcome reporting* may be a reason for the differences in the choice of response criteria. The choice of the outcome time to transformation to acute myeloid leukemia (AML) is potentially problematic due to its dependence on AML definitions used. For example, 32% of patients in the trial of Fenaux and co-workers had AML according to the WHO criteria at the beginning of the study.[4] Lastly, the high heterogeneity observed (even if a random effects analysis was performed) also limits the strength of the evidence and should, therefore, be given more consideration.

Aside from these issues, there are several errors in the Methods section. Based on the Results section, we conclude that the authors accepted any response definition used by the authors and not only the criteria of the International Working Group (IWG).[5] The method of meta-analysis used was the "generic inverse variance