5-azacitidine prolongs overall survival in patients with myelodysplastic syndrome: a systematic review and meta-analysis

CRD summary
This well-conducted review found that hypomethylating agents, particularly 5-azacitidine, improved survival and other outcomes compared with conventional care, but were associated with significant adverse events. These conclusions are likely to be reliable.

Authors' objectives
To assess the role of hypomethylating agents in patients with myelodysplastic syndrome and to determine whether they offer a survival benefit over conventional care.

Searching
PubMed, The Cochrane Library and LILACS were searched to March 2009. Search terms were reported. Relevant conference proceedings were screened from 2002 to 2008. Databases of ongoing and unpublished studies were searched. References of included studies and reviews were searched. No language or publication restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared hypomethylating agents (5-azacitidine, decitabine) to conventional care in patients with myelodysplastic syndrome were eligible for inclusion. The primary outcome was overall survival. Secondary outcomes were early mortality at three months, treatment-related mortality, time to transformation to acute myeloid leukaemia (AML) or death, haematologic response, freedom from red blood cell transfusions and adverse events.

Included trials assessed 5-azacitidine and decitabine. Control interventions consisted of best supportive care in three studies and either best supportive care, low-dose cytarabine or intensive chemotherapy in the other. Median age ranged from 67 to 70 years. In three trials at least 70% of patients were considered to have high-risk myelodysplastic syndrome according to the International Prognostic Scoring System. In the other study fewer than half of the patients were assessed using these criteria and half were considered high-risk.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality based on criteria of allocation concealment, allocation generation and blinding. Disagreements were resolved through referral to a third reviewer.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RR) for dichotomous data or hazard ratios (HR) for time to event data, together with 95% confidence intervals (CIs). Authors were contacted for additional information, where necessary. Disagreements were resolved through referral to a third reviewer.

Methods of synthesis
Summary relative risks and hazard ratios were estimated using the Peto fixed-effect model in the absence of heterogeneity and DerSimonian and Laird random-effects model where there was heterogeneity. Heterogeneity was assessed using $X^2$ and $I^2$. Sensitivity analyses were used to assess the effect of study quality on effect estimates. The effect of drug type was assessed using mixed-effect meta-regression.

Results of the review
Four RCTs reported in five publications (n=952) were included in the review. Only one trial reported adequate
allocation generation. Three trials reported adequate allocation concealment.

Treatment with hypomethylating agents led to improved overall survival compared with conventional care (HR 0.72, 95% CI 0.60 to 0.85; three RCTs). There was substantial heterogeneity between studies ($I^2=53\%$). When analysis was restricted to the two trials that assessed 5-azacitidine, the results remained significant (HR 0.67, 95% CI 0.54 to 0.83). Results were not significant in the one trial that assessed decitabine. The quality of allocation concealment did not impact on the results.

Hypomethylating agents were associated with prolonged time to AML transformation or death (HR 0.69, 95% CI 0.58 to 0.82; four RCTs), improved complete response (RR 7.63, 95% CI 1.41 to 41.17; four RCTs), improved partial response (RR 6.01, 95% CI 2.93 to 12.32; four RCTs), haematologic improvement (RR 3.06, 95% CI 1.09 to 8.6) and improved overall response (RR 5.72, 95% CI 1.60 to 20.39; four RCTs). There was no difference in early mortality at three months (four RCTs) or red blood cell transfusions between treatment groups. Treatment with hypomethylating agents was associated with a significantly higher rate of grade 3/4 adverse events (RR 1.21, 95% CI 1.10 to 1.33; three RCTs). The only outcomes for which significant heterogeneity was found were complete response, haematologic improvement and overall response.

**Authors’ conclusions**
Compared with conventional care, treatment with hypomethylating agents and specifically 5-azacitidine prolonged overall survival and time to acute myeloid leukaemia transformation or death, despite increased treatment-related mortality and lack of difference in early mortality. Treatment with both 5-azacitidine and decitabine improved the rate of complete response, partial response, haematologic improvement and overall response. Treatment was associated with significant adverse events.

**CRD commentary**
The review addressed a focused question supported by clearly defined inclusion criteria. An appropriate literature search was conducted with attempts to minimise language and publication bias. Appropriate steps were taken to minimise bias and errors at all stages of the review process. Study quality was assessed using relevant criteria, but results were presented only for some of the items assessed. The methods used to synthesise studies were appropriate and included relevant subgroup analyses.

The authors’ conclusions were supported by data and are likely to be reliable, although the small number of included studies and heterogeneity between studies for the primary outcome should be considered.

**Implications of the review for practice and research**
- **Practice**: The authors stated that 5-azacitidine should be highly considered in the treatment of patients with high-risk myelodysplastic syndrome.
- **Research**: The authors stated that further studies were needed to establish the exact role of decitabine compared to 5-azacitidine in patients with myelodysplastic syndrome.

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**Bibliographic details**

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.