Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte-colony stimulating factor: a systematic review

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CRD summary
This review found that, in patients with cancer receiving chemotherapy for solid tumours or malignant lymphoma, the risk of all-cause mortality was decreased with use of granulocyte-colony stimulating factor, although the risk of acute myeloid leukaemia or myelodysplastic syndrome was increased. The reliability of these results is unclear, primarily because of the small sample sizes of the included studies.

Authors' objectives
To assess the risk of acute myeloid leukaemia/myelodysplastic syndrome in patients with cancer receiving chemotherapy for solid tumours or malignant lymphoma.

Searching
MEDLINE, EMBASE and the Cochrane Library (including DARE) were searched (January 1990 to October 2008). The National Guidelines Clearinghouse and conference proceedings from the American Society of Clinical Oncology and the American Society of Hematology were scanned. References of all eligible articles were checked.

Study selection
Eligible studies included patients with cancer receiving chemotherapy for solid tumours or malignant lymphoma randomly allocated to granulocyte-colony stimulating factor in addition to chemotherapy or chemotherapy alone. Follow-up of at least two years was required. Studies in which patients received stem cell or bone marrow transplants or had an initial diagnosis of leukaemia were excluded. Primary outcomes were risk of acute myeloid leukaemia, myelodysplastic syndrome and overall survival, disease free survival or all cause mortality.

Patients in included studies had Hodgkin's disease, non-Hodgkin's lymphoma, breast, germ cell, endometrial, urothelial or non-small cell lung cancer; they were treated with a range of chemotherapy regimens. Granulocyte-colony stimulating factor used was filgrastim in most studies; lenograstim was used in the remainder.

The number of reviewers performing study selection was unstated.

Assessment of study quality
Study design was not assessed using a validated tool, but comparability of chemotherapy regimens in each treatment arm was considered as a potential source of bias.

Data extraction
Numbers of patients with acute myeloid leukaemia, myelodysplastic syndrome and all cause mortality were extracted to generate relative risks (RRs) and absolute risks. Information on type of cancer, comparability of chemotherapy regimen in different arms, chemotherapy relative dose intensity and total dose were also extracted to explore heterogeneity.

Two reviewers extracted data with discrepancies resolved by consensus.

Methods of synthesis
Pooling was undertaken using the Mantel-Haenszel method with weighting by inverse variance. Both fixed and random models were employed to calculate pooled relative risks with 95% confidence intervals (CIs). Regression and subgroup analyses were used to explore heterogeneity, which was measured using $I^2$ and tested with $\chi^2$. Publication bias was assessed by examining funnel plot asymmetry and use of both Begg's and Egger's tests.
Results of the review
Twenty-five studies (12,804 patients) were eligible with a median follow-up of 53 months.

Overall risk of acute myeloid leukaemia or myelodysplastic syndrome was increased with use of granulocyte-colony stimulating factor (RR 1.92, 95% CI 1.19 to 3.07), although risk of all-cause mortality was decreased (RR 0.90, 95% CI 0.86 to 0.94). Heterogeneity was not statistically significant and was not explained by cancer type or variation in regimen type between treatment and control arms. Regressions showed statistically significant (p<0.05) relationships between mortality and planned relative dose intensity, actual relative dose intensity and difference in actual relative dose intensity. Results were not sensitive to choice of fixed-effect or random-effects models.

There was evidence of funnel plot asymmetry for acute myeloid leukaemia or myelodysplastic syndrome.

Authors' conclusions
Overall risk of all-cause mortality was decreased with use of granulocyte-colony stimulating factor, although the risk of acute myeloid leukaemia or myelodysplastic syndrome was increased. Greater reductions in mortality were observed with greater chemotherapy dose-intensity.

CRD commentary
This review was based on a comprehensive search and used appropriate methods for pooling. However, the nature of the evidence and review limitations made it difficult to determine to what extent these results were due to chance. The quality of trials on which the review was based was not assessed. Small study sample sizes coupled with low event rates resulted in the pooling of small imprecise effects engendering considerable uncertainty. In addition, time to event data was not extracted, which resulted in potential aggregation biases.

Although the author's conclusions reflect the results, they may not be reliable.

Implications of the review for practice and research
The authors did not state any implications for practice or further research

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