

The Role of Granulopoiesis-Stimulating Factors in the Treatment of Malignant Lymphoma: Recent Update of a Comprehensive Meta-Analysis

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| Origin of Study | Germany |
| Type of Study | META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS |
| Objectives | Determine the effectiveness of granulopoiesis-stimulating factors (granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) in the primary prevention of febrile neutropenia and infections or improvement in quality of life, tumor response, and overall survival in the treatment of malignant lymphoma |
| Study Design | <p>The Cochrane Library, MEDLINE, EMBASE, and smaller bibliographic databases were searched. Additionally, Internet-accessible databases of ongoing clinical trials and conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology were searched, and experts in the field were contacted.</p> <p>Randomized controlled trials comparing parenteral application of granulopoiesis-stimulating factors versus placebo or no treatment in adult and elderly patients with malignant lymphoma undergoing chemotherapy were included in this review. Both study arms had to receive the same chemotherapy and the same supportive care. Both full-length articles and abstracts, as well as unpublished data, were included.</p> <p>Eligibility and quality assessment, data extraction, and analysis were done in duplicate. All authors were contacted to obtain missing data.</p> |
| Patients | Out of 16 eligible studies, 12 clinical trials with 1,823 randomized patients older than 16 years of age who underwent treatment for pathologically confirmed non-Hodgkin's lymphoma or Hodgkin's disease were included in the meta-analysis. |
| Observations | Compared with no prophylaxis, granulopoiesis-stimulating factors significantly reduced the relative risk for neutropenia in seven trials, febrile neutropenia in four trials, and infections in nine trials; there was no evidence that granulopoiesis-stimulating factors decrease infection-related mortality, improve tumor response, or improve overall survival: |

Odds of Granulopoiesis-Stimulating Factors Effecting a Change in Patients With Malignant Lymphoma

| PARAMETER | NUMBER OF CLINICAL TRIALS | NUMBER OF PATIENTS | RELATIVE RISK | CONFIDENCE INTERVAL |
|-----------------------------|---------------------------|--------------------|-------------------|---------------------|
| Neutropenia | 7 | 1,013 | 0.67 | 0.60–0.73 |
| Febrile neutropenia | 4 | 360 | 0.74 | 0.62–0.89 |
| Infections | 9 | 1,292 | 0.74 | 0.64–0.85 |
| Infection-related mortality | 9 | 1,051 | 1.37 | 0.66–2.32 |
| Complete response | 10 | 1,584 | 1.02 | 0.94–1.11 |
| Overall survival | 9 | 1,437 | 1.00 ^a | 0.86–1.16 |

^a Hazard ratio

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The relative risk of bone pain and allergic skin reactions was significantly increased in the group treated with G-CSF or GM-CSF. One study evaluated quality of life and did not show any differences between the study groups.

Conclusions

The benefit of granulopoiesis-stimulating factors in the treatment of malignant lymphoma appears to be limited to endpoints related directly to neutrophil recovery (neutropenia, febrile neutropenia, and infections).

There is no evidence that G-CSF or GM-CSF improves tumor control, as measured by tumor response and overall survival.

The inclusion of recently published studies up to August 2003, with 389 additional patients, confirmed the results of the authors' previous meta-analysis.

Discussion

A meta-analysis of 12 randomized controlled trials in the treatment of malignant lymphoma showed that granulopoiesis-stimulating factors reduced the relative risk of neutropenia, febrile neutropenia, and infections. There was no evidence, however, that G-CSF or GM-CSF improved tumor response, overall survival, or freedom from treatment failure.

The trials compared treatment with standard, nonmyeloablative chemotherapy with supportive care plus G-CSF or GM-CSF (1 µg/kg per day given subcutaneously prior to the onset of neutropenia) with identical chemotherapy and supportive care but without G-CSF or GM-CSF. The 12 trials involved a total of 1,823 patients, all older than 16 years of age and with biopsy-proven Hodgkin's disease or non-Hodgkin's lymphoma.

In addition to randomization, Bohlius and colleagues considered several other quality-assessment measures. They included concealment of allocation; blinding of patients, clinicians, and outcome assessors; reporting of withdrawals and dropouts; and intention-to-treat analysis. Time-to-event data (overall survival and freedom from treatment failure) were calculated as hazard ratios. Binary data were calculated as relative risks and risk differences with the Mantel-Haenszel method in the fixed-effect model.

Compared with no prophylaxis, G-CSF and GM-CSF significantly reduced the relative risk for neutropenia (odds ratio, 0.67; 95% CI: 0.60–0.73), febrile neutropenia (odds ratio, 0.74; 95% CI: 0.62–0.89), and infections (odds ratio, 0.74; 95% CI: 0.64–0.85). There was no evidence, however, that G-CSF or GM-CSF reduced infection-related mortality during chemotherapy (odds ratio, 1.37; 95% CI: 0.66–2.32), improved overall survival (hazard ratio, 1.00; 95% CI: 0.86–1.16), or improved the incidence of a complete response (odds ratio, 1.02; 95% CI: 0.94–1.11).

Key Points

- The benefits of G-CSF and GM-CSF given as primary prophylaxis in patients with malignant lymphoma undergoing conventional chemotherapy are restricted to endpoints directly related to neutrophil recovery.
- These endpoints are reductions in the relative risk for neutropenia, febrile neutropenia, and infection.
- There is no evidence that G-CSF or GM-CSF improve tumor control, overall survival, or freedom from treatment failure in these patients.

References

Bohlius JF, Greb A, Schwarzer G, Reiser M, Engert A: Cochrane Haematological Malignancies Group. The role of granulopoiesis-stimulating factors in the treatment of malignant lymphoma: recent update of a comprehensive meta-analysis. Poster presented at the 45th Annual Meeting of the American Society of Hematology; December 6–9, 2003; San Diego, Calif. Abstract 1804.