Review: Prophylactic use of granulocyte colony–stimulating factor reduces febrile neutropenia and short-term mortality in cancer

Kuderer NM, Dale DC, Crawford J, Lyman GH. **Impact of primary prophylaxis with granulocyte colony–stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review.** J Clin Oncol. 2007;25:3158-67.

Clinical impact ratings: Hematol/Thrombo ★★★★★☆☆ Infectious Disease ★★★★★★☆ Oncology ★★★★★★☆

QUESTION

In adult patients with cancer who are receiving chemotherapy, does primary prophylactic use of granulocyte colony–stimulating factor (G-CSF) reduce febrile neutropenia and early mortality?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Cancerlit, Cochrane Database of Systematic Reviews and Central Register of Controlled Trials, and Database of Abstracts of Reviews of Effect through December 2006; conference abstracts (American Society of Clinical Oncology and American Society of Hematology); references of relevant articles; and experts.

Study selection and assessment: Randomized controlled trials (RCTs) that compared primary G-CSF prophylaxis (given during the first chemotherapy cycle and before neutropenia onset) with placebo or no treatment in adult patients with cancer receiving conventional-dose chemotherapy for a solid tumor or malignant lymphoma. Use of G-CSF was initiated 1 to 3 days after completion of chemotherapy during a cycle and continued until neutrophil recovery. Studies of granulocyte-macrophage colony–stimulating factor were excluded. 17 RCTs (n = 3493, age range 15 to 90 y) met the selection criteria: 10 used filgrastim, 6 lenograstim, and 1 pegfilgrastim. Study quality was poor (Jadad scale ≤ 2) in 9 RCTs.

Outcomes: Febrile neutropenia. Secondary outcomes included infection-related mortality, mortality during the chemotherapy period (early mortality), relative dose intensity (RDI) of chemotherapy, and pain (bone or musculoskeletal).

MAIN RESULTS

Use of G-CSF before onset of neutropenia reduced febrile neutropenia, infection-related mortality, and early mortality but increased bone pain (Table). The RDI of delivered chemotherapy was higher with G-CSF (standardized mean difference 8.4%, range 2.8 to 20.0, P = 0.001). No significant subgroup differences were reported for tumor type, age group, use of prophylactic antibiotics, or use of secondary G-CSF prophylaxis among control groups. All types of G-CSF reduced febrile neutropenia.

CONCLUSION

In adults with cancer who are receiving chemotherapy, primary prophylactic use of granulocyte colony–stimulating factor reduces febrile neutropenia, infection-related mortality, and short-term mortality and increases dose intensity of delivered chemotherapy but also increases bone pain.

Source of funding: National Institutes of Health and Amgen Inc.

For correspondence: Dr. N.M. Kuderer, University of Rochester Medical Center, Rochester, NY, USA. E-mail nicole_kuderer@urmc.rochester.edu. ■

Primary G-CSF prophylaxis vs placebo or no treatment (control) in adults with cancer who have a solid tumor or malignant lymphoma and are receiving chemotherapy*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		G-CSF	Control		
Febrile neutropenia†	15 (3182)	22%	40%	46% (33 to 57)	6 (5 to 8)
Infection-related mortality‡	12 (2917)	1.5%	2.8%	45% (10 to 66)	80 (54 to 365)
Early mortality‡	13 (3122)	3.4%	5.7%	40% (17 to 57)	44 (31 to 104)
				RRI (CI)	NNH (CI)
Bone pain†	14 (3029)	20%	10%	302% (116 to 652)	4 (2 to 9)

*G-CSF = granulocyte colony–stimulating factor; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from RR and control rate in article.
†Based on a random-effects model.
‡Based on a fixed-effects model.

COMMENTARY

G-CSF has modest effects in minimizing the depth and duration of chemotherapy-induced neutropenia. However, it is expensive, requires daily injections, and can cause musculoskeletal pain. The key question is whether G-CSF improves patient outcomes.

The systematic review by Kuderer and colleagues helps to answer this question. First, not only is febrile neutropenia reduced by G-CSF, but both infection-related mortality and overall mortality during the chemotherapy period are reduced by nearly one half. This refutes the argument that G-CSF reduces fever but does not decrease life-threatening infections. Second, the RDI of chemotherapy was significantly higher in patients receiving G-CSF. For patients receiving palliative care, lowering the dose or frequency of chemotherapy to ameliorate neutropenia may be acceptable. However, when the goal of chemotherapy is tumor eradication, increasing evidence supports the intuitive notion that if more chemotherapy is delivered, antitumor effects are improved (1).

How then should this information be translated into clinical practice? The American Society of Clinical Oncology guidelines support the use of G-CSF as primary prophylaxis with chemotherapy regimens that induce febrile neutropenia with a frequency of ≥ 20% and if no other equally effective regimen is available (2). This seems like a reasonable approach, recognizing that patients with comorbid conditions or for whom maintaining dose intensity is essential might benefit from G-CSF even with less myelosuppressive chemotherapy.

A final consideration is the increasing use of pegylated G-CSF (pegfilgrastim), which only needs to be given once per chemotherapy cycle. Only 1 of the 17 trials evaluated this newer agent. However, given the data suggesting equivalent (or superior) effects of pegfilgrastim on neutropenia (3), it is likely that similar benefits will accrue with this agent.

David A. Frank, MD, PhD
Dana-Farber Cancer Institute and Harvard Medical School
Boston, Massachusetts, USA

References

1. **Budman DR, Berry DA, Cirrincione CT, et al.** J Natl Cancer Inst. 1998; 90:1205-11.
2. **Smith TJ, Khatcheressian J, Lyman GH, et al.** J Clin Oncol. 2006;24:3187-205.
3. **Holmes FA, O'Shaughnessy JA, Vukelja S, et al.** J Clin Oncol. 2002;20: 727-31.