Acute Myeloid Leukaemia or Myelodysplastic Syndrome in Randomized Controlled Clinical Trials of Cancer Chemotherapy with Granulocyte Colony-Stimulating Factor: A Systematic Review

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Study Overview:

Granulocyte colony-stimulating factor (G-CSF) has been shown to reduce chemotherapy-induced neutropenia and related complications in cancer patients receiving chemotherapy. G-CSF is also administered to enable the delivery of highly haematotoxic dose-intense and dose-escalating regimens. In a small proportion of patients, myelosuppressive chemotherapy or radiotherapy have been recognised to cause secondary acute myeloid leukaemia (AML), and recently, concerns have been expressed regarding an increased risk of AML and myelodysplastic syndrome (MDS) in patients receiving chemotherapy with G-CSF support.

This systematic literature review aimed to assess AML/MDS risk in cancer patients receiving myelosuppressive chemotherapy with or without G-CSF support in a sufficiently sized population. Data were analysed from 25 randomised clinical trials (RCTs) in 12,804 patients with solid tumours or lymphoma randomised to chemotherapy with (n = 6058) or without G-CSF support (n = 6,746). In order to be eligible, trials had to report AML/MDS or all secondary malignancies, as well as survival or mortality data; ≥ 2 years of follow-up were required.

Weighted summary measures of relative risk (RR) or absolute risk (AR) were calculated using the Mantel-Haenszel method. The primary outcome was the incidence of AML/MDS during the reporting period; secondary outcomes included occurrence of other secondary malignancies and deaths over the same period.

Key Findings:

- Median follow-up was 54 months; 80% of studies used filgrastim and 20% lenograstim.
- In 23 RCTs reporting AML/MDS, there were 65 cases of AML/MDS; crude rates were 0.79% in the G-CSF arms and 0.36% for controls.
- Meta-analysis of these 23 RCTs demonstrated an increased relative risk for AML/MDS in patients with G-CSF support vs those without (RR 1.92; 95% confidence interval [CI] 1.19 to 3.07; p = 0.007; AR increase 0.41%; 95% CI 0.10% to 0.72%; p = 0.009).
- The association between G-CSF and AML/MDS was strongest in studies where patients in the G-CSF arms were planned to receive a higher total chemotherapy dose, and non-significant in those with the same planned dose in both arms.
- In 11 RCTs reporting secondary malignancies, there were 229 cases; crude rates were 3.28% among patients in the G-CSF arms and 3.25% among controls.
- Meta-analysis of these 11 RCTs showed no increased risk of secondary malignancies in patients receiving G-CSF compared with those not receiving growth factors (RR 1.01;

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95% CI -0.002 to 1.30; p = 0.94; AR increase 0.00%; 95% CI -0.002% to 0.009%; p = 0.94).

- Among patients receiving G-CSF, 30.46% died; in control patients the rate was 31.11%.
- Meta-analysis yielded a relative risk of overall mortality of 0.90 (95% CI 0.86 to 0.94; p < 0.001); the corresponding AR reduction was -3.40% (95% CI -2.00% to -4.80%; p < 0.001).
- The RR of mortality was more markedly reduced in studies with higher planned dose intensity in the G-CSF arm; in studies with the same dose in both arms, the reduction was not statistically significant.
- In the 16 RCTs that reported administered chemotherapy dose intensity, relative and absolute dose intensity were 12% and 10% higher with G-CSF support vs no G-CSF.
- There was a significant association between both relative (p = 0.015) and absolute (p = 0.027) increases in delivered relative dose intensity (RDI) and reduced mortality with G-CSF support. No significant association was observed between RDI and RR for AML/MDS or secondary malignancies.

Conclusions:

This systematic review of 25 RCTs in cancer patients randomised to chemotherapy with or without G-CSF support found an increased risk of AML/MDS in patients receiving G-CSF. However, as RDI was also reported to be higher in patients with growth factor support, the authors concluded that it was not possible to distinguish between the effects of G-CSF and the effects of a higher delivered dose of leukaemogenic chemotherapy agents. G-CSF was associated with greater reductions in overall mortality, which is likely due to better disease control in patients receiving dose-intense or dose-dense chemotherapy with G-CSF support. The reduction in mortality was approximately 10 times greater than the increase in AML/MDS risk.

http://www.ncbi.nlm.nih.gov/pubmed/20385991

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