Re: Adverse Effect on Bone Marrow Protection of Prechemotherapy Granulocyte Colony-Stimulating Factor Support

de Wit et al. (1) conducted a prospective phase III trial in which some patients with breast cancer who were receiving higher than conventional doses of chemotherapy received both prechemotherapy and postchemotherapy granulocyte colony-stimulating factor (G-CSF), while others received G-CSF only postchemotherapy. They reported a correlation between the incidence of thrombocytopenia and the administration of prechemotherapy G-CSF for 5 days. They suggest that G-CSF before chemotherapy may worsen the toxic effects on bone marrow, although they did not observe any detrimental effect on the leukocyte or red blood cell counts (1). G-CSF treatment has long been linked to an increase in the incidence of thrombocytopenia, which was generally explained by the achievement of a higher dose intensity of chemotherapy with G-CSF (2,3) or as being disease related (4). Recent studies (5-7) where growth factors were administered to healthy donors to mobilize peripheral blood stem cells suggest that G-CSF might have a direct adverse effect on platelet counts. In these studies, while no significant decrease in platelet counts was noted after administering G-CSF for 5 days, individuals who received 10 days of G-CSF showed a close to 30% decrease from pretreatment platelet values prior to the apheresis (5,6).

In the study by de Wit et al., patients in the prechemotherapy and postchemotherapy G-CSF treatment group received growth factors for at least 13 days per cycle compared with 7 days in the postchemotherapy-only group. Total days actually on G-CSF for either group is not reported in the study. It would thus be possible that the difference in the total days on G-CSF treatment may partially explain the higher incidence of thrombocytopenia in the group that received prechemotherapy and postchemotherapy growth factor treatment. To support the hypothesis of de Wit et al., it would be interesting to assess the marginal toxicity of a group of patients treated with prechemotherapy G-CSF alone, which was not included in their trial. We have recently reported a feasibility trial of prechemotherapy G-CSF, without postchemotherapy growth factors, to prevent further dose delays in patients with a prior episode of prolonged neutropenia while they were undergoing standard-dose chemotherapy for breast cancer (8). We found a significant increase in prechemotherapy neutrophil counts in a 3-week chemotherapy schedule, while no adverse effect was noted on platelet counts and hemoglobin levels. Since in our hands this short (5 days) prechemotherapy course of G-CSF did not have adverse effects on bone marrow, the difference in the doses of chemotherapy or in the total days on G-CSF compared with the study by de Wit et al. may explain the observed increase in the incidence of thrombocytopenia in patients who received prechemotherapy and postchemotherapy G-CSF treatment.

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References


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Response

We appreciate the critical comments by Ribas et al. According to their hypothesis of a direct adverse effect on platelet count by granulocyte colony-stimulating factor (G-CSF), one would not expect to observe increased thrombocytopenia in cycle 1, since the prechemotherapy G-CSF stimulation in that cycle consisted of no more than 5 days preceding the first course. In Table 4 of our paper (1), however, it can be seen that the increased thrombocytopenia in cycle 1 is of the same magnitude as that in cycles 2-6.

Second, a direct adverse effect of G-CSF would be particularly observed at day 1 of cycles 2-6, which is the time of the maximum stimulation following 7-10 days of postchemotherapy G-CSF support at a dose of 5 mg/kg once per day and, after a short period of rest, another 5 days of prechemotherapy G-CSF...