Myeloid Toxicity in Breast Cancer Patients Receiving Adjuvant Chemotherapy: What Is the Appropriate Use of Filgrastim?

To the Editor: Wolff et al[1] report that the hyperleukocytosis event observed in a 67-year-old white woman treated with preoperative dose-dense doxorubicin and cyclophosphamide for four cycles followed by paclitaxel for four cycles, at first supported by pegfilgrastim 6 mg subcutaneously (SC) on day 2, "raises concerns about the potential overutilization of pegfilgrastim in some patients."[1] The same authors suggest that after registering a high day 1 absolute neutrophil count (ANC) it could be safer and simpler "to switch from pegfilgrastim support to just a few doses of filgrastim, as five or fewer doses of filgrastim might be enough to support adjuvant chemotherapy."[2] Of course, we agree with the observations reported by Wolff et al.[1]

We have previously hypothesized[2] that 4 every other day filgrastim injections might be sufficient to support the dose-dense combination chemotherapy regimen, citing our favorable findings of this filgrastim schedule (days 6, 8, 10, 12) in conjunction with a biweekly chemotherapy regimen including cisplatin, epirubicin, folinic acid, and fluorouracil administered to patients with advanced gastric cancer.[3] This filgrastim schedule exerted an acceptable protection from hematological toxicity. In fact, 22% of patients experienced neutropenia grade 3 and 4 respectively, and only two patients (3.4%) had grade 3 febrile neutropenia.

Paclitaxel followed by gemcitabine, a regimen generally not related to a high risk of febrile neutropenia, has been reported to be well tolerated in advanced breast carcinoma, even when given as an every 2-week schedule (paclitaxel 150 mg/m^2, gemcitabine 2,500 mg/m^2).[4] Grade 3 neutropenia was registered in 12% of patients, grade 4 in 17% of patients, and only one patient presented two episodes of febrile neutropenia that resolved with standard therapy and did not require granulocyte colony-stimulating factor (G-CSF) support.[4] Probably, neither paclitaxel at 175 mg/m^2 every 2 weeks would require G-CSF support, although we think that the use of two prophylactic filgrastim injections, on days 8 and 12, could reduce adverse effects, prevent chemotherapy delay, and contemporarily improve the patient's quality of life.

In our study,[2] when we evaluated the role of alternative filgrastim dosing schedules for early-stage breast cancer patients treated with relatively high-dose epirubicin and cyclophosphamide (EC), G-CSF was administered from day 8, 24 to 48 hours before the expected nadir, because the onset of myelosuppression by anthracyclines usually takes place 7 days after administration, and within 24 hours of starting G-CSF injection, neutrophils are rapidly released from the marrow into the circulation.[5] The G-CSF schedules were as follows: (1) 480 μg/d SC days 8 to 14; (2) 480 μg/d SC days 8, 10, 12, and 14; (3) 300 μg/d SC days 8 to 14; (4) 300 μg/d SC days 8, 10, 12, and 14; and (5) 300 μg/d SC days 8 and 12. Filgrastim, regardless of the five tested schedules, significantly reduced the incidence of neutropenic fever ($P = .0007$) and stomatitis ($P = .04$), the need for antibiotics ($P = .003$), the number of delayed courses ($P < .0001$), and the number of cycles requiring dose reductions ($P = .002$) compared with control. As myelopoietic support to EC, no significant differences were found between the five different filgrastim schedules; the short schedule (filgrastim 300 μg/d on days 8 and 12) produced results similar compared with the daily or every-other-day schedules in all the safety end points evaluated.

Using prophylactic filgrastim for a maximum of 7 consecutive days, we observed that the mean peak of ANC exceeded approximately 5 times the upper limit of normal, which indicated that, as prophylaxis, the conventional administration of filgrastim and, as a consequence, the use of pegfilgrastim would probably be not necessary during EC or moderately intensive chemotherapy.[2] Furthermore, compared with daily filgrastim administration, schedule 5 demonstrated less grade 1 to 3 bone pain (53% *v* 29%, respectively; $P = .01$) and less grade 1 to 2 fever (24% *v* 8%, respectively; $P = .04$). In addition, we have found that anemia tended to progressively worsen during chemotherapy with increasing G-CSF dosage, and that the hemoglobin decrease was minimal with the shortened filgrastim schedule (schedule 5).[6] Despite the small number of patients in each group (about 50) and the low power of the study, our findings deserve further investigation in larger randomized clinical trials, in order to improve efficacy, reduce adverse effects, and reduce cost.

Finally, considering the widespread use of CSFs in breast cancer women receiving adjuvant chemotherapy, we agree with Burstein[7] that it is crucial to assure a continue surveillance to these patients to characterize short- and long-term myeloid toxicity of CSFs.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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