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Pegfilgrastim

A Viewpoint by Frankie Ann Holmes

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Pegfilgrastim, administered once per chemotherapy cycle on day 2, provides an answer to the vexing problem of neutropenia that results in potentially life-threatening infection, or more often an unwanted, inconvenient and hastily arranged hospitalisation for intravenous antibiotics.

By pegging a big molecule of polyethylene glycol to the amino end of the filgrastim molecule, the resultant pegfilgrastim becomes so large that, unlike filgrastim, it cannot be filtered by the kidney. The only other way to excrete pegylated filgrastim is by binding to the granulocyte colony-stimulating factor receptor on the granulocytes - so called 'receptor-mediated clearance'. This unique feature means that patients cannot be overdosed with pegfilgrastim. Drug levels remain high when granulocyte counts are low (and stimulate granulocyte recovery). When granulocyte counts increase, the granulocytes bind pegfilgrastim and the level of pegfilgrastim rapidly declines.

Two interesting consequences of 'receptor-mediated clearance' were seen in the clinical trials. First, there was no 'overshoot' in granulocyte recovery, as was seen with daily filgrastim. Second, the continuous exposure of pegfilgrastim to the myeloid cells resulted in higher nadir counts than those of filgrastim, resulting in a halving of the incidence of neutropenic fever. The later phenomenon suggests expansion of the myeloid reserve.

In our studies with the highly myelosuppressive regimen of doxorubicin 60 mg/m^2 with docetaxel 75 mg/m^2,[1] an average of 11 daily injections of filgrastim were needed for granulocyte recovery compared to the single injection of pegfilgrastim on day 2. The study by Green et al.[2] further expanded the utility of this once-a-cycle drug by showing that a fixed dose of 6mg was equivalent to the weight-based dosing we used in our trial.[1]

Despite the continuous presence of pegfilgrastim, however, the intensity of clinical and laboratory abnormalities were similar to those we expect of filgrastim; namely, mild-to-moderate bone pain and transient elevations of uric acid, alkaline phosphatase and lactose dehydrogenase.

The cost of the drug, roughly equivalent to nine or ten doses of filgrastim (but without the administration fees and time for office visits) as well as its extended duration of action mean that it will not be useful for weekly chemotherapy regimens. Nevertheless, those of us using 'mini-courses' of filgrastim from days 5 to 10 only, instead of starting on day 2, may have acheived a false sense of economy by cheating the bone marrow of the extra 'lead time' to accelerate myelopoesis and augment bone marrow reserve, both critical to the necessary dose-intensity to potentially cure our patients. ▲

References

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2. Green M, Koelble H, Baselga E, et al. A randomized, double-blind, phase 3 study evaluating fixed-dose, once-per-cycle pegylated filgrastim (SD/01) vs daily filgrastim to support chemotherapy for breast cancer [abstract no. 90]. 37th Annual Meeting of Clinical Oncology; 2001 May 12-15; San Francisco.