International Journal of Clinical Pharmacy (2019) 41:619–620
https://doi.org/10.1007/s11096-018-0752-3

LETTER TO THE EDITOR

Optimal timing for pegfilgrastim administration in Japanese breast cancer patients receiving intermediate-risk chemotherapies: response to study by Hayama et al.

David H. Henry[1] · Derek Weycker[2] · Mark Bensink[3] · Prasad Gawade[3] · Rajesh Belani[3]

Received: 19 September 2018 / Accepted: 8 November 2018 / Published online: 5 April 2019

Febrile neutropenia (FN) is a potentially life-threatening side effect of myelosuppressive chemotherapy. Recognizing the effectiveness of colony-stimulating factor (CSF) in reducing the risk and consequences of FN, National Comprehensive Cancer Network (NCCN) guidelines recommend CSF prophylaxis when FN risk is high (> 20%) based on either the chemotherapy regimen alone or a combination of the chemotherapy regimen and patient risk factors [1]. Among the CSFs currently available in the US, pegfilgrastim—which requires one dose per cycle, and is available in a prefilled syringe or on-body injector—is by far the most commonly used prophylactic CSF agent in clinical practice [2].

Because pegfilgrastim induces proliferation of myeloid progenitor cells, which may be especially sensitive to myelosuppressive drugs, prescribing information specifies that pegfilgrastim should not be administered between 14 days before and 24 h after administration of myelosuppressive chemotherapy. Moreover, most clinical trial data support use of pegfilgrastim (6 mg) approximately 24 h following completion of chemotherapy. NCCN guidelines state that "[b]ased on clinical trial data, pegfilgrastim [6 mg] should be administered the day after chemotherapy (category 1)", where category 1 indicates that the recommendation is "based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate." [1]

With this as context, in a recent issue Hayama et al. [3] presented a retrospective cohort study suggesting that pegfilgrastim prophylaxis (3.6 mg) between cycle day 3 and cycle day 7 (i.e., between day 2 and day 6 following completion of chemotherapy on day 1) may reduce the risk of FN relative to pegfilgrastim prophylaxis the day after chemotherapy (i.e., on cycle day 2). While we commend the authors for investigating this topic, we believe interpretation of their results is hindered by a lack of critical information. Importantly, we believe that their study design and analyses are flawed, which calls into question the findings of their study. Accordingly, we caution decision makers to carefully review these results within the context of all the available evidence on this topic and consider our specific concerns detailed below.

1. The authors did not describe the baseline characteristics of the study population within the prophylaxis subgroups of interest. Without this information, the reader is unable to ascertain whether, and to what extent, there were systematic differences between patients who received pegfilgrastim on cycle day 2 versus cycle days 3-7. In addition, important baseline characteristics—such as prior chemotherapy/radiation, recent surgery, regimen intensity, and performance status—that are known risk factors for FN, and thus could confound study results, were not described.
2. The authors did not differentiate between primary prophylaxis (i.e., initiation of prophylaxis in cycle 1) and secondary prophylaxis (i.e., initiation of prophylaxis after cycle 1 following an FN event) in multivariable analyses. Again, use of primary or secondary prophylaxis is reasonably expected to align with pegfilgrastim administration day and FN risk, and thus further confound study results.
3. With items 1 and 2, the influence of these and other unobserved or unaccounted for confounders may be magnified given the relatively small sample size of the study (cycle day 2: n = 11; cycle days 3–7: n = 76). For

✉ Derek Weycker
dweycker@pai2.com

[1] Penn Medicine, Abramson Cancer Center, Pennsylvania Hospital, Farm Journal Building, 2nd Floor, 230 West Washington Square, Philadelphia, PA 19106, USA

[2] Policy Analysis Inc. (PAI), Four Davis Court, Brookline, MA 02445, USA

[3] Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, USA

example, the authors note that pegfilgrastim administration day was fixed for patients during their chemotherapy course (based on their physicians' ambulatory practice day). It is unknown whether, and to what extent, differences in physician characteristics, case-mix, and/or treatment patterns between prophylaxis groups might impact study results. Evidence that study results may be influenced by confounding is suggested by the finding that the crude incidence proportion for FN was higher with (vs. without) prophylactic use of fluoroquinolones (30% vs. 14%; derived values, not reported in article), a finding that does not align with current understanding of protective effect of antibiotic prophylaxis [4].

4. While it appears that FN risk was evaluated during the chemotherapy course (it is not stated in the article), it is unknown whether the total number of chemotherapy cycles, and thus time at risk, varied across prophylaxis subgroups (range in study population, 1–11 cycles). Differences in time at risk could be due to reduced chemotherapy discontinuation in one group versus the other, or differences in the split between primary prophylaxis and secondary prophylaxis. Furthermore, time-dependent variables—such as chemotherapy dose reduction, dose delay, and discontinuation, and severe neutropenia—which could impact both pegfilgrastim use and course-level risk of FN, were not evaluated or considered in multivariable analyses.
5. In this observational study of 87 Japanese breast cancer patients, pegfilgrastim dose was 3.6 mg, likely because of the generally smaller meter squared size of the Japanese women. This may limit the external validity of these results outside Japan where patients routinely receive pegfilgrastim dose of 6 mg. It is also important to note that a randomized clinical trial of 351 breast cancer patients failed to demonstrate that pegfilgrastim dose of 6 mg administered on day 4 was more efficacious than day 2 [5].

In summary, we believe that the findings of Hayama et al. in breast cancer patients receiving intermediate-risk chemotherapies should be interpreted with caution and within context of the growing body of evidence on the effectiveness of pegfilgrastim by day of administration. With this, we also believe that additional research employing robust designs, appropriate sources of data, sufficient sample size and presentation of all the information necessary for the proper interpretation of findings is warranted for examining this challenging and important topic.

Funding Funding for the preparation of this letter was provided by Amgen Inc. to Policy Analysis Inc. (PAI).

Conflicts of interest Mark Bensink Ph.D., M.Sc., M.Ed., Prasad Gawade, Ph.D., and Rajesh Belani, M.D. are employed by Amgen Inc. Derek Weycker, Ph.D. is employed by PAI. David Henry, M.D. is employed by Penn Medicine.

References

1. Crawford J, Becker PS, Armitage JO, Blayney DW, Chavez J, Curtin P, Dinner S, Fynan T, Gojo I, Griffiths EA, Hough S, Kloth DD, Kuter DJ, Lyman GH, Mably M, Mukherjee S, Patel S, Perez LE, Poust A, Rampal R, Roy V, Rugo HS, Saad AA, Schwartzberg LS, Shayani S, Talbott M, Vadhan-Raj S, Vasu S, Wadleigh M, Westervelt P, Burns JL, Pluchino L. Myeloid growth factors, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15(12):1520–41.
2. Weycker D, Bensink M, Lonshteyn A, Doroff R, Chandler D. Risk of chemotherapy-induced febrile neutropenia by day of pegfilgrastim prophylaxis in US clinical practice from 2010 to 2015. Curr Med Res Opin. 2017;33(12):2107–13.
3. Hayama T, Sakurai K, Miura K, Washinosu S, Tsuboi S, Uchiike A, Yoshida Y, Takei M. Optimal timing for pegfilgrastim administration in Japanese breast cancer patients receiving intermediate-risk chemotherapies. Int J Clin Pharm. 2018;40(5):997–1000.
4. Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, Stuart N, Rea D, Bower M, Fernando I, Huddart R, Gollins S, Stanley A. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med. 2005;353(10):988–98.
5. Loibl S, Mueller V, von Minckwitz G, Conrad B, Koehne CH, Kremers S, Forstbauer H, Linder M, Nekljudova V, Moebus V. Comparison of pegfilgrastim on day 2 vs. day 4 as primary prophylaxis of intense dose-dense chemotherapy in patients with node-positive primary breast cancer within the prospective, multi-center GAIN study: (GBG 33). Support Care Cancer. 2011;19(11):1789–95.