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Biosimilar pegfilgrastim and adherence to guidelines for chemotherapy-induced neutropenia and infections in cancer patients

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Dear Editor,
Febrile neutropenia (FN) and severe neutropenia are the most common infective complications in cancer patients receiving cytotoxic chemotherapy and may result in severe sepsis, septic shock and mortality [1]. Other consequences are reduced chemotherapy dose intensity, hospitalizations, and increased treatment costs [2]. Primary or secondary prophylaxis with granulocyte colony-stimulating factors (G-CSFs) reduces the incidence of FN and infections, and is associated with decreased FN-related hospitalization, and increased chemotherapy dose intensity, with consequent improvement in overall survival [3].
The major international guidelines recommend G-CSF for patients assigned to chemotherapy regimens associated with high risk (>20%) of FN, or for patients with additional FN risk factors (*e.g.* advanced age, previous FN, advanced disease) [4-6]. Notwithstanding these recommendations, widespread underuse of G-CSF is amply documented in the literature [7-9]. Underuse takes the form of failing to prescribe these medications when indicated or, more commonly, prescribing short-acting forms (*e.g.* filgrastim, lenograstim) for an insufficient number of days, so that neutrophils recovery after nadir is delayed or incomplete [7-9].
The 2019 Italian AIOM (Associazione Italiana Oncologia Medica) guidelines noted the "deep-rooted" clinical practice of administering daily G-CSF for "a limited number of days" and therefore suggested that clinicians may consider this option after discussion with their patients, even though it was admitted that there was no evidence that short duration was as effective as the guideline-recommended duration (until neutrophils count exceeds $1x10^9$/L, typically 9-14 days): a clear case of the tail (entrenched clinical practice) wagging the dog (so-called evidence-based guidelines) [10]. It is likely that short-acting G-CSF is often administered for just a few days because of the inconvenience of daily administration over 10-14 days.
A recent meta-analysis found that in the real world - as opposed to the trial setting - once-per-cycle G-CSFs (generally pegfilgrastim) were more effective at preventing FN than daily G-CSFs, in relation to the widespread under-dosing of daily G-CSFs [11]. Thus, pegfilgrastim emerges as preferable to daily G-CSF both in terms of convenience and efficacy, although it is not appropriate for weekly chemotherapy regimens [12].
Link et al. found that adherence to G-CSF indications improved in Germany after publication of the 2010 EORTC guideline update but remained significantly better in comprehensive cancer centres than other hospitals, and also varied with the type of cancer being treated, and the specialisation of the oncologist [13]. Link et al. emphasized the need for continuing medical education aimed at oncologists to promote adherence to guidelines on G-CSF administration [13].

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A comparative analysis of G-CSF use for FN in Germany, France, Italy, Spain, and the UK, found that the mean absolute cost of a 14-day course of filgrastim and biosimilar filgrastim, and a single dose of pegfilgrastim was 1794, 1336 and 1415 euro, respectively, at 2012 prices. For a 10-day course, filgrastim and biosimilar filgrastim would have cost 1282 and 955 euro, respectively, but the cost of pegfilgrastim would not have changed [14]. In their survey of clinical practice in Italy, Barni et al. found that fewer than six doses of daily G-CSF were administered in 86% of cycles, and fewer than four doses were given in nearly half the cycles. A median of 4 (range 1-10) daily G-CSF doses was administered [8]. Clearly, with dosing schedules like this, the cost of a daily G-CSF course will be very much less than the cost of a pegfilgrastim course, but with the inevitable consequence of poorer outcomes.

We are extremely concerned about the negative consequences of widespread G-CSF underuse in clinical practice and urge the implementation of (and attendance at) continuing medical education initiatives that inform oncologists of the importance of adhering to G-CSF administration guidelines. The recent authorization in Europe of biosimilar pegfilgrastim - which has the same indications as reference pegfilgrastim - may provoke an across-the-board fall in G-CSF prices to hopefully incentivize oncologists to better adhere to administration guidelines for all G-CSF pharmaceuticals, and abandon the practice of using short-acting G-CSFs for just a few days.

Conflict of interest

All authors, who contributed equally to the paper, have advised Accord Healthcare, Italia, SrL on chemotherapy-induced febrile neutropenia and infections in cancer patients. All authors also declare that they have not received any financial support for this work.

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