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Support Care Cancer (2016) 24:4835–4837
DOI 10.1007/s00520-016-3430-9

LETTER TO THE EDITOR

Managing neutropenia by pegfilgrastim in patients affected by relapsed/refractory multiple myeloma treated with bendamustine-bortezomib-dexamethasone

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Received: 12 April 2016 / Accepted: 26 September 2016 / Published online: 10 October 2016
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Dear Editor,

Febrile neutropenia (FN) is a serious side effect of chemotherapy, and even when it does not result in significant morbidity, mortality, and costs, it normally leads to a delay in subsequent chemotherapy treatments [1]. Suboptimal delivery of chemotherapy and reduced relative dose intensity (RDI) adversely affects long-term cancer outcome and survival [2]. FN is a surrogate marker for infections during chemotherapy and is characterized by an absolute neutrophil count (ANC) <1000/mmc and a single body temperature of >38.3 °C or a sustained temperature of ≥38 °C for more than 1 h [1, 3]. Risk of FN is dependent on both patient-specific factors (e.g., type of cancer, disease stage, co-morbid conditions, and age) and the myelotoxicity of the chemotherapy regimen. Once an episode of FN occurs, the risk of FN increases in subsequent chemotherapy cycles [4].

Recombinant granulocyte colony-stimulating factors (G-CSFs) have been developed to stimulate proliferation and differentiation of neutrophils in patients receiving chemotherapy.

The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend the use of G-CSF as primary prophylaxis (PP) when the overall FN risk is greater than 20 % following myelosuppressive chemotherapy, and secondary prophylaxis (SP) following FN or a dose-limiting neutropenic events [4, 5].

Pegfilgrastim is a pegylated long-acting recombinant form of G-CSF which extends the half-life, requiring less frequent dosing than non-pegylated G-CSF [6]. It is indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of FN [5]. Pegfilgrastim is cleared via a neutrophil-mediated system and requires only a single dose administered subcutaneously once per chemotherapy cycle [6–8].

Multiple myeloma (MM) in advanced phases of disease may be managed by regimens combining agents not frequently employed in early phases of treatment (e.g., anthracyclines, alkylating agents, etc), which have significant myelotoxicity. Bendamustine is a bifunctional alkylating agent that produces both single and double strand breaks in DNA, which has shown good results in association with bortezomib and dexamethasone in heavily pretreated patients [9], but in this schedule myelotoxicity is the main expected side effect [10]. In this context, G-CSFs are often necessary to warrant an effective treatment, counteracting the risks of febrile neutropenia. Their use is bound to frequent evaluation of neutrophil counts which may not be easily performed by patients in home care. Avoiding severe neutropenia by prophylactic long-acting G-CSF, as pegfilgrastim, seems particularly useful in this setting of patients.

The objective of this retrospective study was to evaluate the efficacy and safety of pegfilgrastim in relapsed and refractory MM patients, in treatment with courses of bendamustine-bortezomib-dexamethasone (BVD), in order to determine whether primary prophylaxis with pegfilgrastim is more effective than that with filgrastim [6, 11–13] in terms of incidence of chemotherapy disruptions due to FN, days of hospitalization, and G-CSF-related extra-hematological side effects.

Methods

From December 2012 to February 2016, 47 patients have been considered (25 male and 22 female) with a median age of

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61.3 years (range 37–83) affected by relapsed and refractory MM, treated with several lines of treatments (median 6, r. 2–11), and refractory to the drugs previously received, who were treated with monthly courses of BVD (bendamustine 90 mg/sqm i.v. days 1 and 2; bortezomib 1 mg/sqm s.c. days 1, 4, 8, and 11; and dexamethasone 20 mg per os days 1, 2, 4, 5, 8, 9, 11, and 12, until progression).

All treatments were performed in our outpatient unit. Twenty-four consecutive patients received pegfilgrastim (6 mg) subcutaneously with a single administration on day +4, as primary prophlyaxis, and they were compared to a historical group of twenty-three consecutive patients in which filgrastim (5 μg/kg/day for at least 3 days) had been given, as primary prophylaxis "on demand," if neutrophils count was $<1000 \times 10^9$ cells/L.

All patients performed blood counts twice weekly and received, from day +8 to day +19, considering "day +1" the day in which the chemotherapy protocol starts, prophylactic oral quinolones and anti-fungal drugs.

Results

In filgrastim group, twenty-three consecutive patients, previously treated with several lines of treatments (median 6, r. 3–11) with a median age of 60.7 years (r. 37–78) have been considered. Nadir neutropenia was registered after a median of 9.1 days (r.8–15), with maximum duration of 13 days (median 9.4 days, r. 7–13); median of nadir neutrophil count was 1.15×10^9 cells/L (range $0.3–1.5 \times 10^9$ cells/L). Median number of filgrastim administrations was 4.2 (r. 3–6). Patients have been evaluated after at least three courses of therapy (r. 3–6). Filgrastim was well tolerated in all patients; main side effects were mild fever and bone pain (6/23, 26 %), treated successfully with paracetamol. Three hospitalizations for pneumonia were needed during filgrastim (median days of hospitalization 15, range 8–19); the patients received intravenous antibiotic treatment with resolution of infectious episodes. Four patients (4/23, 17.3 %) disrupted chemotherapy schedules because of neutropenia.

In pegfilgrastim group, twenty-four consecutive patients, previously treated with several lines of treatments (median 6, r. 2–10) with a median age of 62.1 years (r. 43–83) have been considered. Nadir neutropenia, registered at day +11, was 1.484×10^9 cells/L (range $1.04–2.33 \times 10^9$ cells/L). During pegfilgrastim, neutropenia, when present, was shorter than during filgrastim treatment, never longer than 8 days (median 5.9 days, r. 4–8), with a consequent reduction of neutropenia-related infections. Only four patients (16.6 %) needed, after pegfilgrastim, a supplement of three administrations of filgrastim. Patients have been evaluated after at least three courses of therapy (r. 3–6). Apart from the advantage of mono-administration, pegfilgrastim was well tolerated in all patients; main side effects were mild fever and bone pain (3/24, 12.5 %), treated successfully with paracetamol. Moreover, no hospitalization was needed during pegfilgrastim. Only two patients (2/24, 8.3 %) disrupted chemotherapy schedules because of neutropenia.

In Italy, the cost of filgrastim 30-MU vial is 95.18–127.95 euro (depending from producer), while the cost of pegfilgrastim 6 mg is 1.489.50 euro. However, this cost has to be considered together with that of hospitalizations, antibiotic usage, and disruptions of scheduled chemotherapy treatments.

Thus, pegfilgrastim was significantly associated with fewer incidence rate of FN-related chemotherapy disruptions (17.3 % in filgrastim group vs. 8.3 % in pegfilgrastim group, $p = 0.3534$ by $\chi 2$ test), fewer days of hospitalization due to FN (median number 15 days in filgrastim group vs. 0 in the pegfilgrastim group), and fewer G-CSF-related extra-hematological side effects (26 % in filgrastim group vs. 12.5 % in pegfilgrastim group, $p = 0.2987$ by $\chi 2$ test), with consequent improvement of quality of life. However, statistical comparison of the two groups (by $\chi 2$ test) was not properly feasible because of the very small sample size.

Conclusions

In conclusions, in patients affected by relapsed and refractory MM, treated with bendamustine-bortezomib-dexamethasone, primary prophylaxis with pegfilgrastim seems to reduce the incidence of chemotherapy disruptions due to FN, and the days of hospitalization. Moreover, it is better tolerated and may increase the opportunity to maintain the planned schedule of treatment. These results make pegfilgrastim and advantageous option in most cases, both in terms of cost-effectiveness and of quality of life. These preliminary observations need to be validated by controlled clinical trials, involving a larger number of patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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