



## Bendamustine and G-CSF support

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We read the manuscript by Cerchione C et al. with particular interest [1]. The use of peg-filgrastim in patients treated with bendamustine in terms of the timing of filgrastim/peg-filgrastim is concerning. Prolonged neutropenia is sometimes anticipated during bendamustine chemotherapy. Cerchione C et al. reported the clinical benefits of peg-filgrastim as the primary prophylaxis for neutropenia [1]. This manuscript reported reduced neutropenic episodes and reduced febrile neutropenia (with or without documented infection) in patients treated with peg-filgrastim compared to those in the control group who were treated with filgrastim. This finding was hypothesized to reduce overall chemotherapy disruptions. We can acknowledge the importance of relative dose intensity (RDI) in the treatment of malignant lymphoma, which is supported by significant evidence. RDI is associated with a higher remission rate and better survival [2]. However, the relationship between RDI and survival in patients receiving bendamustine treatment and R-CHOP has not yet been fully revealed. In addition, grade 3–4 neutropenia occurred in only 44% of patients in a phase II study conducted by Czuczman MS et al. [3]. Grade 3–4 febrile neutropenia was observed in 6.1% of patients in another phase II study [4]. Thus, we might consider using peg-filgrastim in a “secondary-prophylaxis” manner, according to the risk assessment of the NCCN Clinical Practice Guidelines (NCCN guidelines®) for myeloid growth factors.

Here, we report the case of an 82-year-old male diagnosed with advanced mantle cell lymphoma and treated with rituximab–bendamustine (RB) therapy. He repeatedly received six courses of RB treatment until achieving complete remission. He did not initially receive G-CSF support during the chemotherapy. However, in his third course of RB therapy, prolonged neutropenia delayed the following course of chemotherapy (Fig. 1). He then received a single dose of each filgrastim and peg-filgrastim during the following chemotherapy course. Thereafter, his treatment course was not affected by chemotherapy disruption owing to the prolonged neutropenia after the fourth course of RB. Additionally, RDI was maintained throughout the following chemotherapy courses. Our case did not require G-CSF/peg-G-CSF support during the first two courses of RB. The first onset of grade 3 neutropenia was observed after the third course of chemotherapy. This suggests that primary prophylaxis with G-CSF/peg-G-CSF is not necessary for all the cases, even in those of elderly patients. Therefore, a secondary prophylactic use of peg-G-CSF seems more reasonable for the chemotherapy-induced neutropenia caused by bendamustine. However, the NCCN guidelines® for myeloid growth factors (Version 2.2017 revised on October 13, 2017) do not evaluate the use of G-CSF for bendamustine-containing regimens.

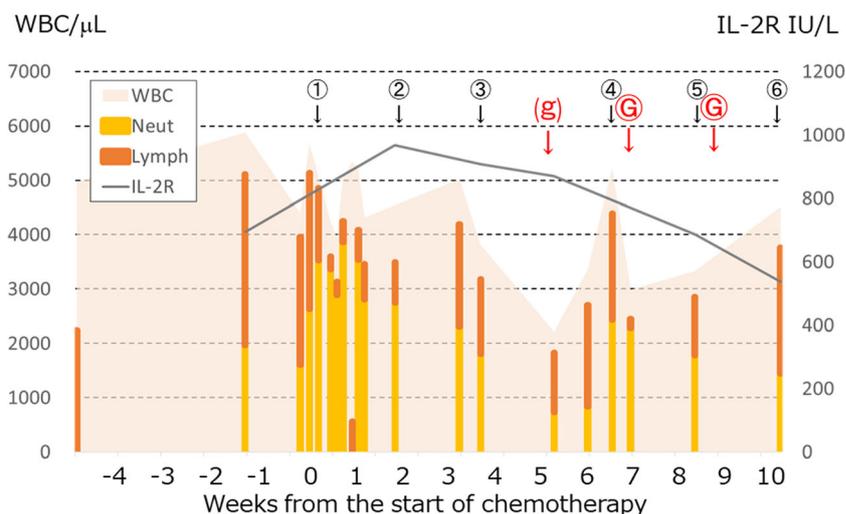
Our case suggests that bendamustine causes prolonged neutropenia during the following course rather than during the initial course. The prevalence of severe neutropenia (grade 3–4) complicated with febrile neutropenia was estimated to be < 10% according to several clinical studies [4] (up to 8.23% based on Japanese post-marketing surveillance data). This frequency of febrile neutropenia does not require routine prophylaxis of G-CSF/peg-G-CSF (NCCN guidelines). Further investigation to evaluate the efficacy of the primary or secondary prophylactic setting of G-CSF is warranted for the RB regimen.

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**Fig. 1** Clinical course of the case. The circled numbers (①–⑥) indicate the chemotherapy course number. The marks (g) and © indicate the subcutaneous administration of 75 µg of filgrastim and 3.6 mg of peg-filgrastim, respectively. The secondary prophylactic peg-filgrastim could prevent treatment disruption after the fourth course (abbreviations: Lymph, lymphocyte; Neut, neutrophil; WBC, white blood cell)



## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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