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Letter to the Editor

A case of Waldenstrom Macroglobulinemia in which intermittent one-day administration cycles of bendamustine were effective for alleviation of nausea and maintenance of remission

Keywords: Waldenstrom Macroglobulinemia, bendamustine, one-day administration, intermittent administration, hepatitis B carrier.

TO THE EDITOR

We have obtained consent from the patient for publication of this case report. The patient was a 73-year-old male. A routine medical checkup in 2008 revealed anemia and he was referred to our department. The laboratory findings at that time were as follows: hemoglobin (Hb), 8.8 g/dL; serum β2-microglobulin, 3.6 mg/mL; serum immunoglobulin M (IgM), 3880 mg/dL. Serum immunoelectrophoresis revealed a positive result for IgM-κ, and bone marrow examination showed an increase in small lymphocytes. The cell surface marker profile was as follows: IgM+, κ+, CD5+, CD10-, CD19+, CD20+, CD22+, CD23-, CD25+), FMC7+ and CD138-. Computed tomographic examination revealed no lymphadenopathy or hepatosplenomegaly. We diagnosed the patient with Waldenstrom Macroglobulinemia (WM). The patient was not tested for the myeloid differentiation factor 88 (MYD88) L256P mutation. The clinical course is shown in the figure. In 2009, the patient became transfusion-dependent, but had no systemic symptoms. In 2010, he developed systemic symptoms, and received treatment with R-COP (rituximab: 375 mg/m^2, cyclophosphamide: 750 mg/m^2, vincristine: 1.5 mg/m^2 and prednisolone: 100 mg for 5 days). This therapy proved ineffective, and the patient received bendamustine (120 mg/m^2/day for 2 consecutive days) in 2011. With this treatment, the patient demonstrated partial response (PR).

Our present patient received 3 antiemetics (palonosetron, dexamethasone (DEXA), and aprepitant). He developed grade (G) 2 delayed-onset nausea, which occurred a few days after administration of bendamustine and persisted for approximately one week. The dosing interval of bendamustine was extended by 3 months and the second cycle was administered. The 3rd and 4th cycles could be administered as prescribed. Bendamustine had to be discontinued due to G3 delayed-onset nausea. He developed disease recurrence and received the 5th and 6th cycles. Due to worsening of the delayed-onset nausea (G3), it became difficult for him to come to the hospital for even 2 consecutive days. In 2013, bendamustine was restarted at the dose of 120 mg/m^2/day on only one day per cycle (from the 7th cycle onward). Bendamustine was administered intermittently for a total of 12 cycles. The patient then exhibited an uneventful clinical course, without nausea, while PR was maintained. However, he developed parkinsonism in May 2016 and died of the disease in August 2016. When he died, PR was still maintained.

The reported incidence from overseas of nausea associated with bendamustine ranges from 17% to 77%.[1,2] The reported incidence in Japan is in the range of 19.2% to 100%[3,4]; thus, the incidence tends to be higher in Japan than overseas. Nausea has been reported to be correlated with the maximum plasma concentration (Cmax) of bendamustine.[5,6] The Cmax was reported to increase in proportion with the dose,[7,8] suggesting that the incidence of nausea may increase in a dose-dependent manner.[7] Dose reduction is likely to reduce the incidence of nausea by decreasing the Cmax. It has been shown that no correlation exists between the dose (Cmax) and the efficacy of bendamustine against the primary disease.[7] It has also been reported that there are no differences in the Cmax among persons of different races,[8,9] but a higher Cmax was reported in a study involving only Japanese,[7] suggesting that this may be the cause of the higher incidence of nausea in Japan. As the half-life of bendamustine is extremely short, even two-day administration per cycle may not cause accumulation of bendamustine or increase the Cmax.[8] Accordingly, if the nausea were only related with the Cmax, no difference in its incidence would be expected between patients receiving two-day administration and those receiving one-day administration. However, in the present case, nausea occurred after two-day administration per cycle, but was alleviated after changing to one-day administration; the Cmax was considered to have remained

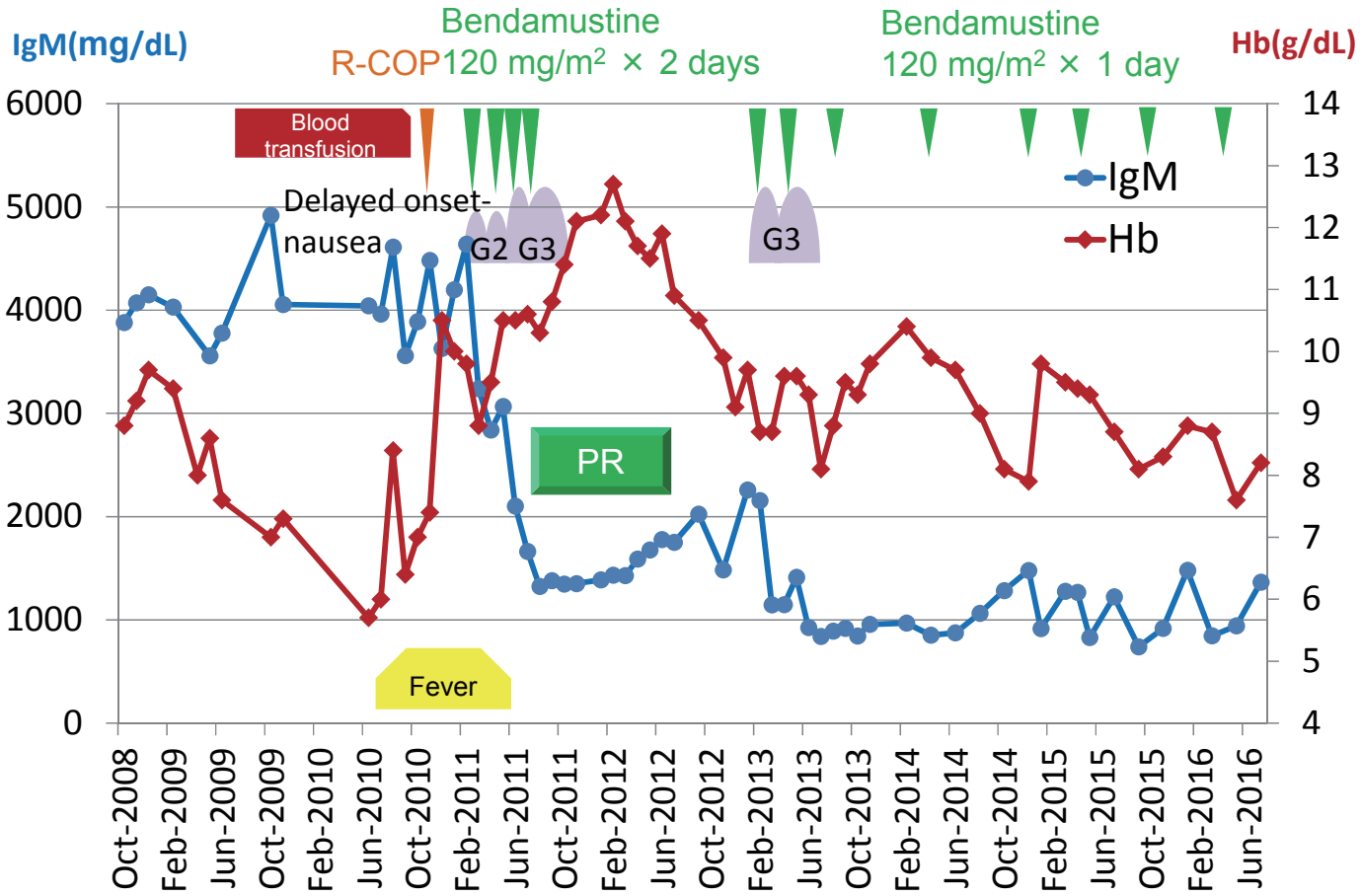

Fig. Clinical course
In October 2009, the patient became transfusion-dependent. In October 2010, he developed systemic symptoms and received R-COP therapy; however, this treatment proved ineffective. Bendamustine therapy was started in February 2011, and PR was achieved. Entecavir was administered, and no subsequent activation of hepatitis B was observed. Palonosetron, DEXA and aprepitant were co-administered as antiemetics. The patient received the 2nd to 4th cycles, but bendamustine had to be discontinued thereafter due to the appearance of delayed-onset nausea. In February 2013, the patient was restarted on bendamustine and received the 5th cycle, but developed delayed-onset nausea after the 6th cycle. From the 7th cycle onward, bendamustine was administered at 120 mg/m^2/day on only one day per cycle. Thereafter, his nausea was alleviated. From the 8th to the 12th cycles, the same dose of bendamustine was administered intermittently in single-day cycles. The nausea did not recur and PR was maintained.

unchanged. The precise underlying mechanisms remain unclear and further investigation is needed. In addition, although dose-reduction criteria have been described for cases with adverse events,[10] no criteria have been established yet for reducing the number of days of administration. This is the first report of such treatment in a patient with hematological malignancy. Intermittent one-day administration per cycle is effective for preventing nausea. There has been only one previous report of one-day administration of bendamustine per cycle in a patient with a solid tumor.[11] Further clinical studies are needed to evaluate the efficacy and adverse effect profile of this regimen by measuring the Cmax and blood concentrations of the drug in patients with hematological malignancies.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this paper.

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