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**LETTER TO THE EDITOR**

# Prolonged lymphocytopenia after bendamustine therapy in patients with relapsed or refractory indolent B-cell and mantle cell lymphoma

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Although bendamustine with or without rituximab has demonstrated remarkable efficacy in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma (B-NHL) and mantle cell lymphoma (MCL),[1–3] previous reports showed that the incidence of lymphocytopenia was higher in patients receiving bendamustine with or without rituximab than in those receiving other conventional cytotoxic chemotherapies such as R-CHOP regimen,[4–7] which triggers opportunistic infections including cytomegalovirus (CMV) reactivation, hepatitis B virus reactivation, varicella zoster virus (VZV) infections and *Pneumocystis jirovecii* pneumonia (PCP).[8–12] However, the duration until recovery of the decreased lymphocytes and CD4-positive T cells to the baseline upon bendamustine treatment is still unclear.[6]

We retrospectively analyzed 56 consecutive patients with relapsed or refractory indolent B-NHL and MCL who received bendamustine (Treakisym) with or without rituximab at our institution between 2011 and 2014. The dose of bendamustine in combination with or without rituximab was 90 mg/m$^2$/day or 120 mg/m$^2$/day on days 1 and 2, respectively. Treatment was given every 28 days for up to six treatment cycles, depending on the response and toxicity. No rituximab maintenance was given. We analyzed their peripheral blood lymphocytes and CD4-positive T-cell counts before, during and after bendamustine treatment, the details of infectious events and their correlations. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Thirty-one patients (55%) were male, with a median age of 63 years (range: 36–86). Twenty patients (35%) had follicular lymphoma, 14 (25%) MCL, 9 (16%) transformed lymphoma, 5 (9%) extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, 4 (7%) small lymphocytic lymphoma, 2 (4%) nodal marginal zone lymphoma and 1 (2%) each had lymphoplasmacytic lymphoma and low-grade B-NHL, unclassifiable. The median number of prior regimens administered was 2 (range: 1–9). Twenty-three (41%) of the 56 patients received rituximab in combination with bendamustine. The median number of bendamustine cycles was 4 (range: 1–6) and the median cumulative dose of bendamustine was 720 mg/m$^2$ (range: 60–1440 mg/m$^2$). The median follow-up period was 9 months (range: 0–33 months).

Before starting bendamustine treatment (that is, at baseline), median lymphocyte and CD4-positive T-cell counts were 1025/μl (range: 270–3420/μl) and 282/μl (range: 83–645/μl), respectively. After the first cycle, they immediately decreased to 545/μl (range: 60–2900/μl) and 190/μl (range: 116–635/μl), respectively. During the period between the completion of bendamustine and starting the next treatment (that is, during observation), the median lymphocyte and CD4-positive T-cell count nadirs were 365/μl (range: 20–1310/μl) and 93/μl (range: 7–178/μl), respectively. Significantly decreased lymphocyte counts were detected in 23 patients who received bendamustine with rituximab compared with 33 patients who received bendamustine alone (median: 260 vs 410/μl, $P = 0.03$). Recovery of lymphocyte and CD4-positive T-cell counts to those at the start of treatment was observed in patients who did not receive the next treatment at 7–9 months after the completion of bendamustine with or without rituximab, and median lymphocyte and CD4-positive T-cell counts were

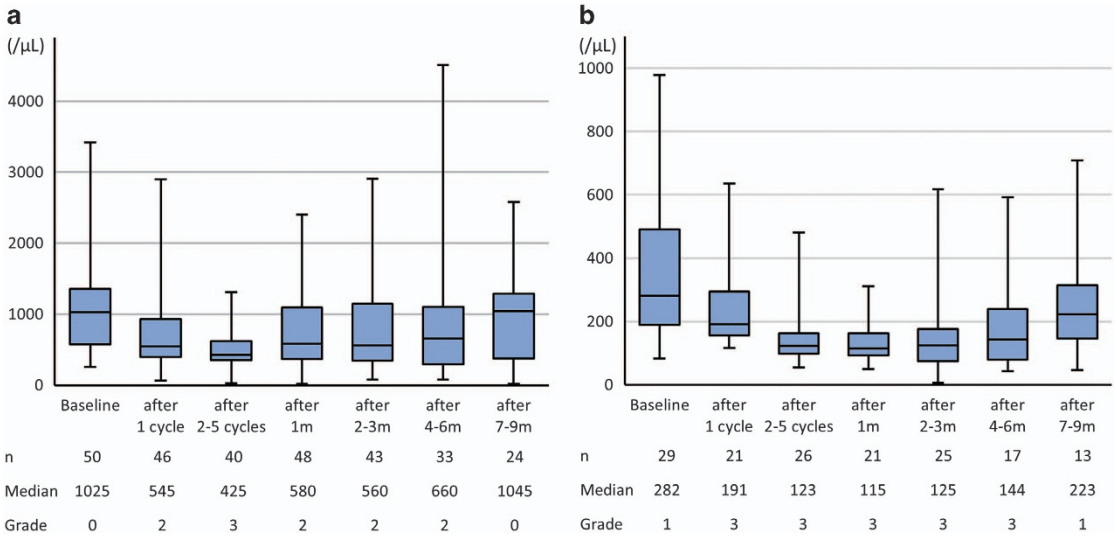


**Figure 1.** Lymphocyte counts and CD4-positive T-cell counts. Box plots of lymphocyte counts (**a**) and CD4-positive T-cell counts (**b**) among patients who were treated with bendamustine with or without rituximab from baseline to 7–9 months after the completion of bendamustine.

**Table 1.** Infectious complications between after starting bendamustine and the last follow-up

| *Patients affected, n (%)* | *During bendamustine* | *During observation* | *During subsequent treatments* | *Total follow-up* |
|---|---|---|---|---|
| *Cytomegalovirus antigenemia* | | | | |
| All grades | 4 (7) | 2 (4) | 9 (16) | 15 (27) |
| ⩾Grade 3 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| *Cytomegalovirus disease (colitis)* | | | | |
| All grades | 0 (0) | 0 (0) | 1 (2) | 1 (2) |
| ⩾Grade 3 | 0 (0) | 0 (0) | 1 (2) | 1 (2) |
| *Pneumocystis pneumonia* | | | | |
| All grades | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| ⩾Grade 3 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| *Varicella zoster virus* | | | | |
| All grades | 0 (0) | 0 (0) | 2 (4) | 2 (4) |
| ⩾Grade 3 | 0 (0) | 0 (0) | 1 (2) | 1 (2) |
| *Hepatitis B virus reactivation* | | | | |
| All grades | 1 (2) | 0 (0) | 1 (2) | 2 (4) |
| ⩾Grade3 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| *Other infections* | | | | |
| All grades | 15 (25) | 8 (13) | | 18 (32) |
| ⩾Grade3 | 3 (6) | 0 (0) | | 3 (6) |

1045/μl (range: 170–2580/μl) and 223/μl (range: 47–709/μl), respectively (Figures 1a and b). In comparison between 1 month and 7–9 months after the completion of bendamustine without rituximab, lymphocyte counts were significantly increased (median: 565 vs 1125/μl, $P=0.003$). On the other hand, with rituximab, lymphocyte counts were not significantly increased (median: 600 vs 780/μl, $P=0.07$).

The number of patients who received prophylaxis at the physician's discretion against PCP, VZV infection and fungal infection were 44 (79%), 37 (66%) and 4 (7%), respectively. Infectious events were observed in 32 patients (57%) during the period between the initiation of bendamustine and the last follow-up (that is, total follow-up). CMV antigenemia was detected in 15 patients (27%), VZV infection in 2 (4%), CMV colitis in 1 (2%) and other infectious complications in 18 patients (32%), namely, fever in 15 (27%), febrile neutropenia in 2 (4%), sepsis in 2 (2%), urinary tract infection in 2 (2%) and oral candidiasis in 1 (2%) (Table 1). Although no statistically significant differences were detected between lymphocytopenia and the incidence of infectious events in this study, mainly because of the small number of patients, all infectious events occurred within 9 months after the completion of bendamustine in patients who received no treatment after bendamustine during follow-up.

In this study, recovery of lymphocyte and CD4-positive T-cell counts to those at baseline was observed at 7–9 months after the completion of bendamustine with or without rituximab. Although statistical significance was not identified, some reports have suggested that the absolute lymphocyte count might be relevant to the development of CMV reactivation[8,9] and hepatitis B virus reactivation.[11] In the patients who received rituximab in combination with bendamustine, it tended to take longer for the lymphocyte counts to recover.

Our analysis revealed that relapsed or refractory patients with indolent B-NHL and MCL showed prolonged lymphocytopenia and low CD4-positive T-cell counts for at least 7–9 months after the completion of bendamustine with or without rituximab. The prophylaxis against PCP and VZV deserves consideration for at least 7–9 months after bendamustine treatment. Further investigations are needed to confirm our results.

## CONFLICT OF INTEREST

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