INTERNAL MEDICINE

□ CASE REPORT □

Peripheral Neuropathy Exacerbated by Lenalidomide in a Patient with Multiple Myeloma

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Abstract

We evaluated a serial change in peripheral neuropathy (PN) severity during treatment with bortezomib (Bor) or lenalidomide (Len) using the Functional Assessment of Cancer Therapy scale/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx). The patient suffered from grade 2 PN and exhibited a dramatic decrease in FACT/GOG-Ntx score after intravenous and subcutaneous Bor therapy. Thereafter, he received seven cycles of Len therapy, which exacerbated existing PN; he experienced mild numbness and exhibited a transient decrease in FACT/GOG-Ntx score. Interestingly, FACT/GOG-Ntx score increased to baseline and numbness was ameliorated during the Len washout period in every cycle.

Key words: multiple myeloma, peripheral neuropathy, lenalidomide, FACT/GOG-Ntx

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Introduction

Lenalidomide (Len) is a second-generation thalidomide analog that has become a cornerstone treatment for multiple myeloma (MM), particularly for patients with relapses or refractory disease. Two prospective randomized studies demonstrated that there was no increase in clinically significant peripheral neuropathy (PN) in relapsed MM patients treated with Len compared with those treated with dexamethasone (1, 2). These studies indicate that unlike bortezomib (Bor) or thalidomide, Len is expected to rarely induce or exacerbate PN (1, 2). Therefore, it has been suggested that Len can be safely administered to patients with existing PN or a history of PN. Although clinicians are aware that Len occasionally aggravates existing PN (3, 4), particularly during early treatment cycles (4), there is little detailed information regarding the clinical course of PN following treatment with Len (i.e., whether Len-induced PN is reversible). We herein describe the detailed clinical course of Bor-induced PN that was transiently, but reversibly, exacerbated following salvage Len administration in a patient with relapsed MM.

Case Report

In April 2009, a 56-year-old Japanese man presented with pathologic vertebral fractures and multiple osteolytic lesions; he was subsequently diagnosed with MM with Bence-Jones protein κ [International Staging System (ISS) Stage 2, Durie-Salmon stage IIIB] and exhibited a normal karyotype and 30% plasma cells on bone marrow (BM) assessment. The patient received one cycle of combination vincristine, doxorubicin, and dexamethasone (VAD) chemotherapy, followed by intravenous Bor and dexamethasone therapy twice weekly (ivBD; Bor, 1.3 mg/m^2; dexamethasone, 40 mg) on days 1, 4, 8, and 11, and thereafter every 3 weeks. Although there was a partial response (PR) to the first cycle, ivBD was discontinued because of the patient developed grade 3 PN, which left him unable to walk without support. Subsequently, the patient received two autologous peripheral blood stem cell transplants (ASCTs), resulting in very good PR. However, he relapsed 15 months after the second ASCT and experienced severe bone pain. BM assessment revealed 9.6% plasma cells. Based on his rapid response to ivBD, he was treated with subcutaneous (sc) BD salvage therapy once

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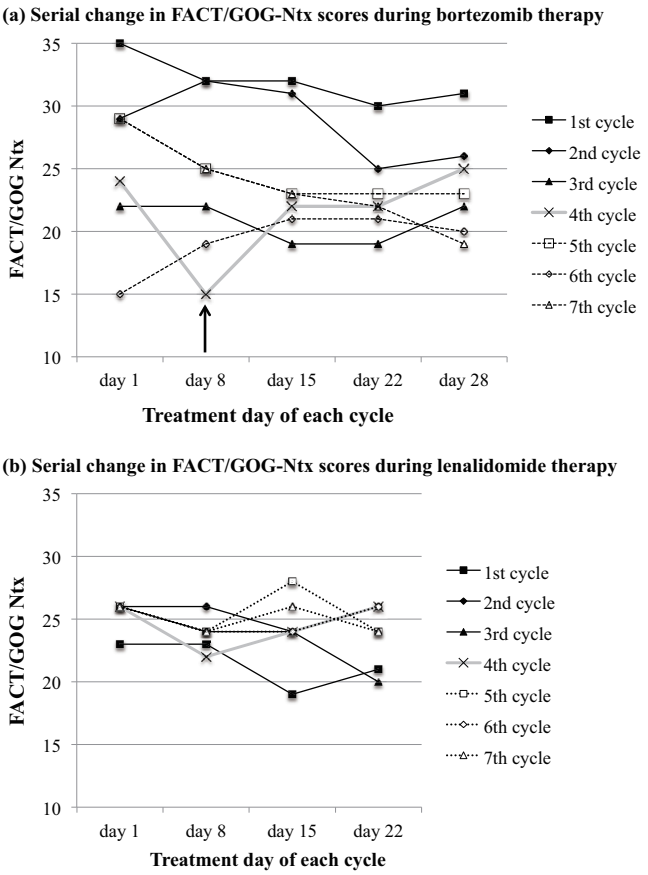

Figure. Serial changes in FACT/GOG-Ntx during (a) scBD therapy and (b) LD therapy. (a) The FACT/GOG-Ntx score decreased from 35 on day 1 of the first cycle to 15 on day 8 of the fourth cycle, resulting in reduction of Bor from 1.3 mg/m^2 to 1.0 mg/m^2. Thereafter, the FACT/GOG-Ntx score varied between 15 and 29 without further decrease. (b) The FACT/GOG-Ntx score was 23 at the start of LD therapy due to Bor-induced PN before Len treatment. The score transiently decreased on days 8, 15, and 22 but recovered to baseline by the start of the next LD treatment cycle.

weekly (Bor, 1.3 mg/m^2; dexamethasone, 40 mg) on days 1, 8, 15, and 22 every 4 weeks, and his PN reduced to grade 1. PN symptoms were scored weekly using the Functional Assessment of Cancer Therapy scale/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) (5), which is comprised of 11 questions rated on a 5-point scale from 0 ("not at all") to 4 ("very much"). An increased total score ranging from 0 to 44 was classified as "improved," whereas unchanged or declining scores was classified as stable/declined (5). The first cycle of scBD significantly decreased his bone pain and reduced the number of plasma cells to 1.6% on BM assessment. After the second cycle of scBD, he reported a mild increase in limb numbness. Figure a shows the serial change in his FACT/GOC-Ntx scores over time. Although the score decreased from 35 to 25 by the end of the second scBD cycle and his PN was still categorized as grade 1 with mildly worsened numbness and tolerable, the treatment was continued without a reduction in Bor because of the significant efficacy of the treatment. However, on day 8 of the fourth cycle of scBD, his FACT/GOG-Ntx score decreased to 15, and his PN exacerbated to grade 2 with aggravation of limb numbness; therefore, Bor was reduced from 1.3 mg/m^2 to 1.0 mg/m^2 (Figure a). The FACT/GOG-Ntx score transiently increased from 15 to 29 on day 1 of the fifth cycle with improvement of limb numbness. However, in January 2012, after seven cycles of scBD, the FACT/GOG-Ntx score decreased to 19 on day 28 of the seventh cycle. We found that the patient's MM had progressed with back pain and elevation of serum κ-free light chain (serum κ-FLC, 2,610 mg/L; λ-FLC, 6.1 mg/L; κ/λ ratio, 427.9). When we compared the mean FACT GOG-Ntx score in the first cycle of scBD treatment with those during subsequent cycles using Tukey's test, the mean of the score in the first cycle (32.0±1.9) was comparable with the mean score in the second cycle (28.6±3.0). However, the means of scores in the third (20.8±1.6), fourth (21.6±3.9), fifth (24.6±2.6), sixth (19.2±2.5), and seventh cycles (23.6±1.2) were significantly lower than the mean score in the first cycle ($p<0.01$). Next, we compared the mean FACT GOG-Ntx score on day 1 with the mean scores on other days during all seven scBD treatment cycles using a Mann-Whitney U-test. There were no significant differences between day 1 and other days. These results demonstrate that existing PN was exacerbated by scBor treatment and was never restored to the baseline by the start of the next scBD treatment.

Subsequently, the patient started Len and dexamethasone therapy every 28 days (LD; Len, 10 mg for 14 days; dexamethasone, 40 mg, daily on days 1, 8, 15, and 22) because of renal dysfunction and persistent grade 2 thrombocytopenia and neutropenia. After the first LD cycle, his back pain disappeared, and κ-FLC dramatically decreased (κ-FLC, 155 mg/L; λ-FLC, 7.4 mg/L; κ/λ ratio, 20.9). He received seven cycles of LD until disease progression without requiring reduction of Len dosage. His PN was transiently exacerbated with mild worsening of limb numbness for several days after the beginning of each LD cycle, but his symptoms improved during the Len washout period of 14 days in each cycle. Figure b shows the serial change in FACT GOG-Ntx scores during the seven LD treatment cycles. At the start of treatment, his baseline score was 23, and grade 2 PN was present from the previous ivBor and scBor treatments. In the first LD treatment cycle, the FACT/GOG-Ntx score decreased from 23 on day 1 to 19 on day 15. Thereafter, the score increased to 26 on day 1 of the second cycle, and the score at day 1 was maintained at 26 as the baseline in subsequent cycles. Similar to the kinetics of the FACT/GOG-Ntx score in the first cycle, the score decreased from 26 on day 1 to 20 on day 22 in the third cycle; 22 on day 8 in the fourth cycle; and 24 on day 8 in the fifth, sixth and seventh cycles. When we compared the mean FACT GOG-Ntx score in the first cycle with those in subsequent cycles using Tukey's test, the mean FACT/GOG-Ntx score in the first cycle (21.5±1.9) was comparable with those in the third (23.5±2.5), fourth (24.5±1.9), sixth (25±1.2) and

seventh cycles (25±1.2), whereas the means of the scores in the second (25.5±1.0, $p<0.05$) and fifth cycles (25.5±1.9, $p<0.05$) were significantly higher than the mean of score in the first cycle (21.5±1.9). These results indicated that the means of FACT/GOG-Ntx scores did not decrease following repeated LD treatments. In addition, the mean FACT GOG-Ntx score on day 1 (just before the start of each LD treatment cycle) was significantly higher than that of other days (25.0±1.0 vs. 23.9±2.1, p=0.046) (Mann Whitney U-test). These results indicated that FACT GOG-Ntx scores decreased with LD treatment on days 8, 15, and 22 but returned to baseline by the start of the next LD cycle. In August 2013, his MM relapsed and rapidly progressed. The patient underwent allogeneic bone marrow transplantation from a related donor following a reduced-intensity conditioning regimen consisting of melphalan (140 mg/m^2), fludarabine (150 mg/m^2), and total body irradiation (4 Gy), but he subsequently succumbed to sepsis and multiple organ failure 15 days after transplantation.

Discussion

One cycle of ivBor induced intolerable severe PN that required treatment cessation, whereas scBor was continued for seven cycles with only mild progression of existing PN. This clinical course was consistent with that of a previous report describing that scBor was associated with decreased PN incidence and severity with equivalent efficacy to ivBD (6). However, our patient's FACT/GOG-Ntx score decreased from 35 to 19 by the end of scBor treatment (Figure a) and was 23 at the start of Len (Figure b). Statistically, despite the reduction of Bor after the fourth cycle of scBD treatment, the means of the FACT/GOG-Ntx scores in the second and subsequent cycles became significantly lower than the mean score in the first cycle ($p<0.01$). In contrast to Bor, although Len exacerbated existing PN, this was only temporary because PN recovered to baseline severity by the time of the next LD cycle. Particularly, the mean FACT GOG-Ntx score on day 1 was significantly higher than that of other days (25.0±1.0 vs. 23.9±2.1, p=0.046). Interestingly, reversibility of PN exacerbation due to Len was clearly evidenced by both the patient's reports of limb numbness and changes in the FACT GOG-Ntx score. In addition, although the FACT/GOG-Ntx score transiently decreased in every treatment cycle, the means of the scores of the third, fourth, sixth, and seventh LD treatment cycles were significantly higher than the mean score of the first cycle. These results might indicate that Bor-induced PN, which did not seem to improve in the short-term observation during scBD treatment, slowly improved after cessation of scBD treatment in the long term, even during LD treatment. Therefore, the means of FACT/GOC-Ntx scores increased in some LD treatment cycles compared to the mean score in the first cycle, although administration of Len mildly and transiently exacerbated PN in each treatment cycle. Although the efficacy of the FACT/GOG-Ntx for evaluating Bor-induced PN is known (7), this report is the first to evaluate PN exacerbation after Len administration. Based on our experience with this patient, physicians should be aware that any exacerbation of existing PN due to Len administration may be reversible and thus will likely improve during the washout period. A large prospective study is required to further assess the efficacy of the FACT/GOG-Ntx to evaluate PN following Len administration, as well as the reversibility of PN exacerbation by Len.

The authors state that they have no Conflict of Interest (COI).

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