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LETTER TO THE EDITOR

Successful Retreatment with Elotuzumab for Multiple Myeloma with Extramedullary Relapse while Being Treated with Lenalidomide and Dexamethasone

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Dear Editor,

The prognosis of multiple myeloma (MM) has markedly improved in the past few years due to the introduction of immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies, and high-dose therapy followed by autologous stem cell transplantation (ASCT); however, even after achieving complete remission, the majority of patients ultimately relapse or their disease progresses relapsed/refractory MM (RRMM). Extramedullary myeloma has been increasing throughout the overall disease course and the prognosis is poor [1]. Treatment selection and sequencing in RRMM and extramedullary myeloma are becoming more complex and clinicians have an increasing number of options when considering suitable treatment regimens for their patients. However, none of the reported trials have included patients who progressed while being treated with lenalidomide and dexamethasone (Ld). We herein present a RRMM patient with extramedullary relapse and progression while being treated with Ld; however, he achieved very good partial remission (VGPR) after being treated with elotuzumab in combination with Ld.

In January 2017, an 80-year-old male with MM (IgG-κ type) following 5 years of treatment with bortezomib and dexamethasone, Ld, and pomalidomide and dexamethasone relapsed for the fourth time with extramedullary renal plasmacytoma. The patient was retreated with a Ld regimen because of the duration and strength of the response to previous Ld. After 3 cycles of Ld, serum and urine M protein levels were undetectable by immunofixation, and a subsequent CT scan revealed a marked reduction in extramedullary renal plasmacytoma. He achieved VGPR and continued Ld. However, in August 2018, after 20 cycles of Ld, the patient suddenly developed nasal congestion with anemia (hemoglobin 7.4 g/dL, normal range: 14–18 g/dL) and hyperproteinemia (total protein 11.0 g/dL, normal range: 6.9–8.2 g/dL). Serum levels of albumin and lactate dehydrogenase were 2.29 g/dL (normal range: 3.9–4.9 g/dL) and 351 U/L (normal range: 106–211), respectively. He concomitantly exhibited worsening renal function with a creatinine level of 4.89 mg/dL (normal range: 0.4–0.8 mg/dL). His serum β2-microglobulin level was 12.8 mg/dl (normal range: 0.9–2.0 mg/dL), and IgG and κ-light chain concentrations were 66 g/L (normal range, 8.7–17 g/L) and 222 mg/dL (normal range, 3.3–19.4 mg/dL), respectively, which were confirmed to be the M protein by serum immunofixation electrophoresis. A CT scan revealed a paranasal sinusoidal tumor and the recurrence of renal plasmacytoma (Fig. 1a, b). Biopsy was performed on the paranasal sinusoidal tumor. A histopathological study demonstrated the diffused proliferation of plasma cells by hematoxylin and eosin staining, and an immunochemical examination showed that the specimen was CD38+, CD138+, CD56+, CD45+, MUM1+, kappa+, and lambda-. Bone marrow aspirate revealed 8% plasma cell infiltration with normal karyotypes. These results suggested the fifth relapse of MM with extramedullary plasmacytoma in the paranasal sinus and kidney. He received a regimen of elotuzumab and Ld (ELd) (elotuzumab, 10 mg/kg, days 1, 8, 15, and 22 during the first two cycles and then on days 1 and 15 starting with the third cycle; lenalidomide 25 mg/day, days 1–21; and dexamethasone 40 mg/day, days 1, 8, 15, and 22). After 4 cycles of this treatment, a subsequent CT scan revealed marked reductions in extramedullary paranasal sinusoidal and

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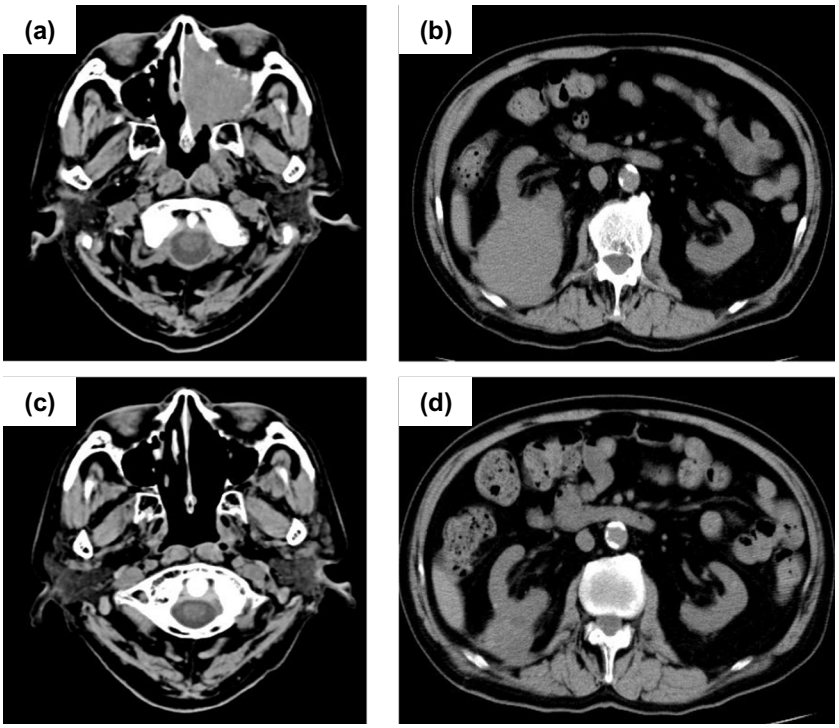

Fig. 1 A CT scan showed a paranasal sinusoidal tumor and the recurrence of renal plasmacytoma (**a**, **b**). After 4 cycles of a treatment with elotuzumab, lenalidomide, and dexamethasone, a subsequent CT scan revealed marked reductions in extramedullary paranasal sinusoidal and renal plasmacytomas (**c**, **d**)

renal plasmacytomas (Fig. 1c, d) with the amelioration of nasal congestion and improved renal function (creatinine level 1.39 mg/dL). Serum IgG and κ-light chain concentrations had also decreased (19.4 g/L and 25.2 mg/dL, respectively). He achieved and maintained VGPR following the ELd regimen for 8 cycles.

Extramedullary myeloma is a highly aggressive disease entity that responds poorly to all treatment modalities, and the optimal sequence of treatment currently remains unknown. The efficacy of monoclonal antibodies, such as daratumumab and elotuzumab, for extramedullary myeloma has not yet been demonstrated. It is important to investigate the pathological or molecular characterization of myeloma cells and consider high-risk features at the time of relapse and its duration, the strength of responses to previous treatments, and previous tolerability in order to guide therapy.

CD45, the first receptor-like protein tyrosine phosphatase expressed on all nucleated hematopoietic cells, is strongly expressed in normal immature proliferative plasma cells, but is weakly expressed in mature resting plasma cells in bone marrow . CD45- MM cells have been more strongly linked to disease progression and poor treatment responses than CD45+ MM cells. Furthermore, CD45- cells were found to exhibit slightly stronger PI3'K activity than CD45+ MM cells [2]. According to Guo et al., signaling lymphocytic activation molecule F7 (SLAMF7)-mediated inhibition involved SH2 domain-containing inositol phosphatase 1 (SHIP-1), a negative regulator of PI3'K, which suggests that stronger PI3'K activity in CD45- MM cells was due to the weaker SLAMF7-dependent activation of SHIP-1 [3]. Elotuzumab is a humanized immunoglobulin G1 immunostimulatory monoclonal antibody against SLAMF7, a glycoprotein expressed in myeloma cells and natural killer cells, but not on normal non-lymphoid tissues . However, the effects of elotuzumab on extramedullary myeloma currently remain unknown. In the present case, CD45+ extramedullary myeloma cells were associated with SLAMF7 and SHIP-1 expression, and thatmight be corrected with successful treatment with elotuzumab.

Treatment selection and sequencing in RRMM are becoming more complex and clinicians have an increasing number of options when considering suitable treatment regimens for their patients. Elotuzumab, in combination with Ld, is one of several regimens recommended by the National Comprehensive Cancer Network for the treatment of patients with RRMM [4]. In addition to ELd, there are currently several combination therapies, such as daratumumab, carfilzomib, and ixazomib, with Ld [5]. However, none of the reported trials included patients who progressed while being treated with Ld. The present case showed relapse and progression while being treated with Ld, and elotuzumab in combination with Ld demonstrated a durable clinical benefit, safety, and tolerability for elderly RRMM patients. Clinical judgment is needed to decide whether a patient may still be sensitive to a treatment strategy consisting of an Ld-containing regimen.

This is the first case report to show that a very advanced extramedullary myeloma patient responded to elotuzumab even after being previously treated with and becoming refractory to Ld. Extramedullary myeloma is increasingly becoming a clinically significant manifestation of MM that appears to have a

distinct pathogenesis, clinical course, immunophenotype, cytogenetic profile, and response to treatment from marrow-restricted myeloma. Therefore, further studies are needed to improve clinical management for the successful treatment of these patients.

Compliance with Ethical Standards Satoko Oka declares that she has no conflicts of interest in the present study.

Kazuo Ono declares that he has no conflicts of interest in the present study.

Masaharu Nohgawa declares that he has no conflicts of interest in the present study.

This article does not contain any studies with human participants performed by any of the authors.

This patient provided his written informed consent to receive each regimen, and treatment was administered according to the principles of the Declaration of Helsinki and this study was approved by the institutional ethics committee.

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