

Daratumumab monotherapy in relapsed and refractory multiple myeloma patients with severely compromised forced expiratory volume in one second

TO THE EDITOR: Daratumumab monotherapy is approved to treat patients with relapsed or refractory multiple myeloma (RRMM) who have previously received three or more treatments, including a proteasome inhibitor and an immunomodulator or presenting with double refractoriness to proteasome inhibitors and immunomodulators [1]. Although daratumumab monotherapy has been introduced in real-world practice based on the results of phase 1 (GEN501) [2] and phase 2 clinical trials (SIRIUS) [3], the results of these clinical trials were limited to individuals with no severe comorbidities according to the trials' design. For example, patients with respiratory impairment indicated by forced expiratory volume in one second (FEV1) of <50% were excluded from the GEN501 and SIRIUS trials. Accordingly, the safety of daratumumab monotherapy would be limited in these patients. Furthermore, the CD38,

which is the target of daratumumab, is not only over-expressed on the multiple myeloma cells [4] but also widely presented on airway smooth muscle cells [5]. Due to general reports that altered CD38 expression on airway smooth muscle cells could contribute to airway hyperresponsiveness [6], the respiratory infusion-related reactions (IRRs), such as bronchospasms or dyspnea, are considered to require particular attention following infusion of daratumumab [2, 3]. Therefore, the administration of daratumumab to patients with FEV1s of <50% could present a difficult challenge. Nevertheless, a clinician could be forced to select a novel agent such as daratumumab for patients who do not fit the selection criteria of clinical trials if there are limited chemotherapeutic options for heavily treated patients with RRMM in real-world clinical practice. Thus, it is important to validate the real-world safety of daratumumab monotherapy for patients with severe comorbidities that make them unfit for clinical trials.

Herein, we report the cases of 3 patients who experienced manageable pulmonary manifestations after the administration of daratumumab monotherapy [7], despite decreased FEV1s of <50% at baseline. This study was approved by the Institutional Review Board of The Catholic University of Korea (KC21RASI0664) and was conducted in accordance with the Declaration of Helsinki.

Table 1. Patient baseline characteristics.

	Case 1	Case 2	Case 3
Age/sex	61/F	71/F	40/M
Type of disease at diagnosis	IgG	IgG	Light chain disease
Light chain type at diagnosis	Kappa	Lambda	Kappa
International staging system at diagnosis	III	II	III
White blood cell count at baseline, $\times 10^9/L$	7.24	2.49	5.12
Absolute neutrophil count at baseline, $\times 10^9/L$	5.06	1.34	4.45
Absolute lymphocyte count at baseline, $\times 10^9/L$	1.15	0.80	0.31
Hemoglobin at baseline, g/dL	12.1	8.6	9.1
Platelet count at baseline, $\times 10^6/L$	111	54	22
Albumin at baseline, g/dL	3.6	2.9	4.1
$\beta 2$ -microglobulin at baseline, $\mu g/mL$	3.76	2.135	N/A
Serum creatinine at baseline, mg/dL	1.52	1.25	0.46
Lactate dehydrogenase at baseline, IU/L (reference, 250–450 IU/L)	429	739	633
Forced expiratory volume at one second at baseline, %	43	40	44
Presence of plasmacytoma at baseline	Yes	No	Yes
Interval from diagnosis to treatment of daratumumab, months	90	47	80
Serum M protein at baseline, g/dL	0.99	3.25	0
Serum kappa/lambda at baseline, mg/day	122.5/14.5	8.14/368.51	1.41/<0.76
Presence high-risk cytogenetics at diagnosis			
del(17p)	Negative	Negative	Negative
t(14;16)	Negative	Negative	Negative
t(4;14)	Negative	Negative	Negative
Other cytogenetic abnormality at diagnosis			
Amp(1q21)	Negative	Positive	Negative
t(11;14)	Negative	Negative	Negative
del(13q)	Negative	Positive	Negative

Abbreviation: N/A, not available.

CASE

Table 1 summarizes the baseline clinical characteristics of the 3 cases. At the baseline pulmonary function test

assessment, the FEV1 was 43%, 40%, and 44% in case 1, case 2, and case 3, respectively. All patients received daratumumab monotherapy at a dose of 16 mg/kg, and the

Table 2. Outcomes of daratumumab monotherapy.

	Case 1	Case 2	Case 3
N of prior treatments lines before daratumumab	4	3	5
Interval from diagnosis to treatment of daratumumab, months	90	47	80
Administered cycles of daratumumab (total time of infusion)	1 cycle (2 times)	5 cycles (13 times)	1 cycle (4 times)
Best response of daratumumab monotherapy	Refractory	Minimal response	Refractory
Survival status	Death at 2 months	Death at 19 months	Death at 1 month
Adverse events, infusion-related reaction			
Dyspnea, grade	2	-	-
CRP elevation, grade	3	-	-
Cause of death	Progression of disease	Progression of disease	Progression of disease

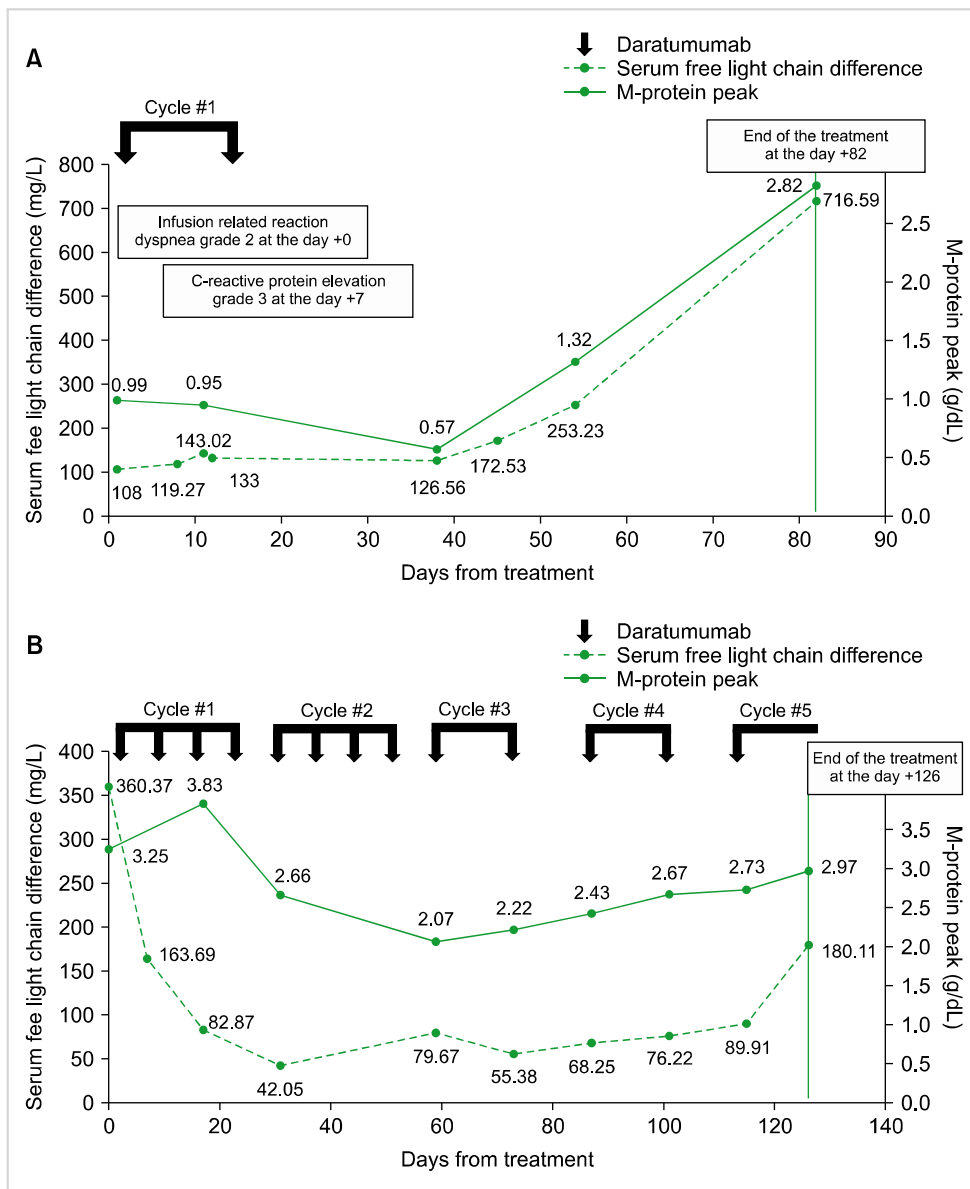


Fig. 1. Treatment course and adverse events of case 1 (A), case 2 (B), and case 3 (C).

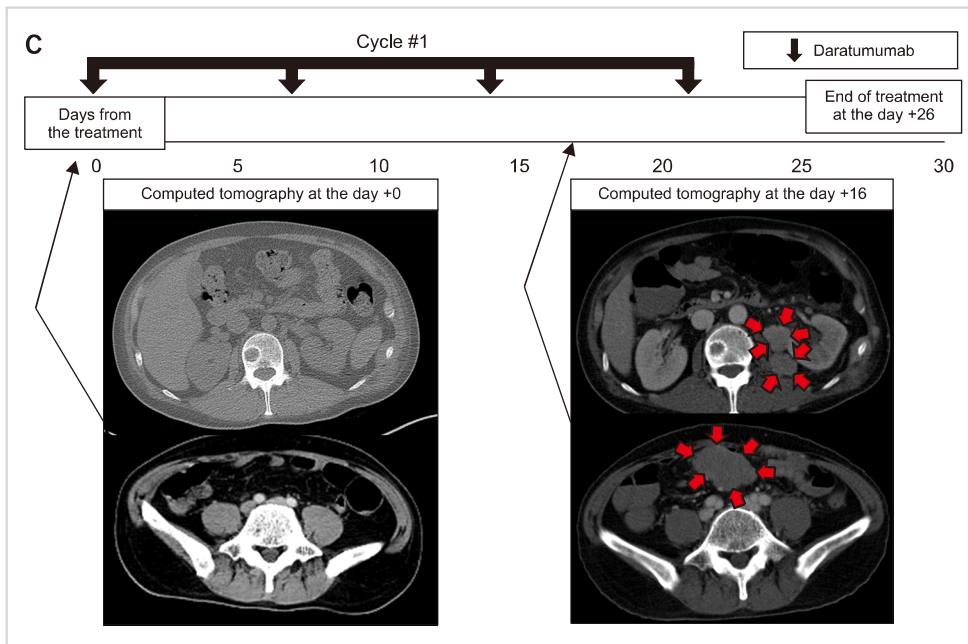


Fig. 1. Continued.

treatment plan was weekly for the first 8 weeks (cycles 1 and 2), then every 2 weeks from 9 to 24 weeks (cycles 3–6), then every four weeks thereafter (cycles 7 and higher). To prevent IRRs, the patients received 100 mg of intravenous methylprednisolone at the first and second daratumumab infusions. Other supportive care and preventive medications were administered as described in our previous reports [8]. The clinical outcomes of the 3 patients are summarized in Table 2. All adverse events were explored based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [9].

Case 1

A 61-year-old female, who was diagnosed with multiple myeloma type IgG-kappa 8 years earlier, had relapsed following first-line treatment with autologous stem cell transplantation after vincristine, doxorubicin, and dexamethasone; second-line treatment consisting of eight cycles of bortezomib and dexamethasone; third-line therapy with lenalidomide plus dexamethasone (RD), and fourth-line treatment with pomalidomide, cyclophosphamide, and dexamethasone (PCD). She also presented with relapsed and refractory response status following 13 cycles of PCD.

Before daratumumab monotherapy, the baseline assessment showed a monoclonal protein level of 0.99 g/dL and serum-free light chain differences of 108.00 mg/L with a predominance of kappa chains. The laboratory and radiological tests did not indicate specific implications related to multiple myeloma. Although an IRR grade 2 dyspnea developed on the first day of daratumumab infusion, this event was spontaneously resolved by supportive care with corticosteroids and antihistamine. She also experienced a grade 3 adverse event of elevated C-reactive protein levels. Therefore, we decided to postpone the second infusion of

daratumumab to a week later than planned. In the second daratumumab infusion, there was no significant IRR. Her course of RRMM was refractory despite two cycles of daratumumab monotherapy, and she died of disease progression (Fig. 1A).

Case 2

A 71-year-old female with multiple myeloma type IgG lambda was diagnosed 3 years earlier and had relapsed. The patient was initially treated with nine cycles of bortezomib, melphalan, and prednisone, which resulted in relapsed and refractory responses. The patient was subsequently treated with 20 cycles of RD, and a partial response was achieved, but the RD course was terminated due to grade 3 neutropenia. Third-line treatment with eight cycles of PCD was administered, and a minimal response was observed, but the patient relapsed. The fourth-line treatment was daratumumab monotherapy.

The monoclonal protein assessment and serum-free light chain differences were 3.25 g/dL and 360.37 mg/L, respectively. Baseline magnetic resonance imaging indicated an L1 compression fracture related to RRMM manifestation. After daratumumab monotherapy, there was no IRR. The best response to daratumumab monotherapy was minimal, with a monoclonal protein value of 2.07 g/dL. However, the disease progressed after five cycles. Despite administering a next-line treatment with thalidomide, cyclophosphamide, and dexamethasone, the patient died due to disease progression (Fig. 1B).

Case 3

A 40-year-old male had kappa light chain multiple myeloma diagnosed 7 years earlier. The patient was treated with two cycles of bortezomib, melphalan, and prednisone, fol-

lowed by autologous stem cell transplantation and tandem allogeneic stem cell transplantation as the first-line treatment. Eight cycles of bortezomib and dexamethasone were administered for the first relapse. He was treated with six RD cycles for the second relapse, which resulted in the partial response, but showed a relapse and refractory response with multifocal bone lytic lesions. Despite the fourth-line treatment with five cycles of pomalidomide and dexamethasone, the patient became refractory, and the multifocal bone lesions progressed. The Fifth-line treatment with carfilzomib-dexamethasone was initiated but was also limited to a refractory response with multifocal extramedullary plasmacytomas (Fig. 1C). The sixth-line treatment was with daratumumab monotherapy.

Baseline computed tomography showed multiple plasmacytomas at the left orbit and periauricular regions, upper back, left apical axilla, abdominal wall, and left thigh (Fig. 1C). Baseline monoclonal protein was negative in electrophoresis, and there was no significant difference (1.41 mg/L) between the quantity of serum-free light chains. During daratumumab monotherapy, there was no IRR, but the patient died due to disease progression.

DISCUSSION

Real-world experience with daratumumab monotherapy has continuously been reported since its approval as a treatment for RRMM [10-13]. The studies highlighted that daratumumab monotherapy was safely administered to patients, including those who did not fit the clinical trials selection criteria. Our previous study reported the favorable efficacy and infusion-related safety of 64 RRMM patients who would be unfit to participate in the GEN501 or SIRIUS due to comorbidities including an Eastern Cooperative Oncology Group Performance Status of ≥ 3 , meningeal involvement, anemia of < 75 g/L, neutropenia of $< 1.0 \times 10^9/L$, thrombocytopenia $< 75 \times 10^9/L$, and renal insufficiency with a glomerular filtration rate of < 20 mL/min/1.73 m². No reported IRRs interrupted the daratumumab schedule, and all IRRs were manageable with supportive care [8].

To the best of our knowledge, this study reports the first daratumumab monotherapy safety profile in patients with decreased lung function demonstrated by an FEV1 $< 50\%$. Although 1 in 3 patients experienced a respiratory IRR, it was manageable with supportive care. The best response of the RRMM patients was limited to less than a minimal response. However, regarding the safety perspective, daratumumab monotherapy might be considered for RRMM patients with FEV1 $< 50\%$. Moreover, recent suggestions to introduce montelukast as pre-medication for daratumumab [14, 15] could be a part of preventive measures on respiratory IRR for patients with low FEV1. This study's case series and recent suggestion for preventive montelukast could contribute to establishing a better cohort study reflecting more reliable real-world outcomes of daratumumab monotherapy.

The present study had several limitations. First, this study

had a limited number of cases, making the results difficult to generalize. Moreover, the treatment efficacy in all patients was disappointing. Therefore, a larger cohort study needs to clarify the efficacy in RRMM patients with pulmonary dysfunction. Finally, the safety of daratumumab monotherapy is not guaranteed in an individual with more severe pulmonary dysfunction since the FEV1 of the patients varied from 40% to 50%.

Conclusively, daratumumab monotherapy should not be considered an absolute contraindication for RRMM patients with 40-50% FEV1 when chemotherapeutic options are limited.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Dasatinib-induced reversible pulmonary arterial hypertension in a pediatric patient with BCR/ABL1+ lymphoblastic lymphoma from chronic myeloid leukemia

TO THE EDITOR: Dasatinib, a second-generation tyrosine kinase inhibitor (TKI), targets many tyrosine kinases, including Src and ABL kinases, whereas imatinib targets only BCR-ABL1. Therefore, dasatinib could be used in the treatment of BCR-ABL1+ chronic myeloid leukemia and BCR-ABL1+ acute lymphoblastic leukemia [1, 2]. In addition, dasatinib inhibits most mutated forms of BCR-ABL1; it can be an effective option for patients who are refractory

to imatinib [3]. Pulmonary arterial hypertension (PAH) is one of the side effects of dasatinib: 0.45–5% of patients who received dasatinib developed PAH in a previous study involving adult populations [4, 5]. As the indications of dasatinib have been extended to pediatric patients, there are growing concerns about dasatinib-induced PAH [6]. To the best of our knowledge, this is the first case of dasatinib-induced PAH in a pediatric patient with BCR/ABL1+ lymphoblastic lymphoma from chronic myeloid leukemia (CML). The Institutional Review Board of the Seoul National University Hospital approved the procedure of reviewing medical records, and the requirement for written consent was waived (H-2002-125-1104).

A 4-year-old girl developed BCR-ABL1+ lymphoblastic lymphoma in the nasal cavity after receiving imatinib for 15 months for CML. At diagnosis of CML, BCR-ABL1 fusion was detected in 94% of cells on the initial bone marrow exam with fluorescence in situ hybridization (FISH). Translocation t(9;22)(q34;q11) was found by multiplex nested reverse transcriptase-polymerase chain reaction (RT-PCR) of bone marrow aspirate and peripheral blood. The initial BCR-ABL1 major International Scale (IS), used for the measurement of residual disease, was 56.4% on bone marrow aspirate. A year and three months after the initiation of imatinib, BCR-ABL1 major IS dropped to 0.1% on peripheral blood. However, a diagnosis of BCR-ABL1+ lymphoblastic lymphoma was made after a soft tissue mass was found in the nasal cavity 17 months after diagnosis of CML. BCR-ABL1 fusion was identified in 99% of cells on endoscopic biopsy and 6.3% of cells on bone marrow aspirate. The diagnosis was made through FISH analysis; real-time quantitative polymerase chain reaction (RQ-PCR) was not done. The patient remained in remission per the bone marrow exam results, without any evidence of lymphoma involvement or exacerbation of CML. The regimen of induction chemotherapy included prednisolone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, and intrathecal chemotherapy. After induction chemotherapy, bone marrow results showed complete response, with BCR-ABL1 fusion detected in 0.3% of cells by FISH and a BCR-ABL1 major IS ratio of 0.07, which was below 0.1. Dasatinib was added, and allogeneic hematopoietic stem cell transplantation (HSCT) from a matched unrelated donor was performed 6 months after diagnosis of BCR-ABL1+ lymphoblastic lymphoma, with busulfan, fludarabine, and etoposide as the conditioning regimen [7]. The last BCR-ABL1 major IS before HSCT was 0.01%, and it went below the detection limit after HSCT. Dasatinib was resumed 3 months after HSCT. One year after HSCT, the patient developed exertional dyspnea. Chest computed tomography (CT) showed mosaic attenuation in both lungs. The dyspnea got worse and resulted in the limitation of ordinary activity to 10 minutes. The dose of dasatinib was then decreased from 70 mg to 60 mg due to persistent moderate neutropenia.

Seven months after the initial symptoms of dyspnea and 21 months after HSCT, the patient presented with fever,