Successful treatment of bortezomib-refractory multiple myeloma derived from monoclonal gammopathy of undetermined significance with dose-adjusted lenalidomide therapy in a patient with concomitant end-stage renal disease due to diabetic nephropathy requiring haemodialysis

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Abstract Malignancy is a fatal complication of end-stage renal disease (ESRD) requiring haemodialysis. However, the successful treatment of haematological malignancies has been rarely reported. We describe the case of a 63-year-old man who presented with IgA-type multiple myeloma (MM; Durie–Salmon stage IIIB) derived from monoclonal gammopathy of undetermined significance concomitant with ESRD due to diabetic nephropathy. First, haemodialysis was initiated before chemotherapy, and bortezomib and dexamethasone were found to be ineffective. Subsequently, 8 courses of dose-adjusted lenalidomide therapy were administered according to the degree of haematological and renal functions. The patient remained

in partial remission without disease progression for 21 months. Thus, lenalidomide therapy is effective for bortezomib-refractory MM concomitant with ESRD.

Keywords Monoclonal gammopathy of undetermined significance · Multiple myeloma · Diabetic nephropathy · Haemodialysis · Dose-adjusted lenalidomide therapy

Background

Heart failure, infection, malignancy and cerebrovascular disease have been reported to be life-threatening and fatal complications in patients with end-stage renal disease (ESRD) who are undergoing haemodialysis [1]. Most malignant tumours originate from the gastrointestinal tract (stomach and colon), kidneys, lungs and thyroid; however, haematological malignancies such as multiple myeloma (MM) are rarely reported [1]. MM is a clinical entity characterised by bone marrow infiltration by plasma cells, resulting in anaemia, skeletal destruction and renal dysfunction [2–4]. The current first-line treatment recommended for MM is bortezomib, lenalidomide or thalidomide [2–6]. The proteasome inhibitor bortezomib and the immunomodulatory drug lenalidomide have been reported to be effective in patients with MM [2–6]. A few previous studies have reported that, in patients undergoing haemodialysis, bortezomib-refractory MM was successfully treated with lenalidomide therapy [7–9]. Here, we report the case of a patient with bortezomib-refractory MM and ESRD who was successfully treated with a dose-adjusted therapy of lenalidomide; haemodialysis was initiated at diagnosis and maintained thereafter.

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Case report

A 63-year-old man presenting with lower-extremity oedema was referred to a regional hospital on 13 September 2006. He was found to have diabetes mellitus (DM) when he was 57 years old, and oral glucose-lowering agents such as an α -glucosidase inhibitor and sulfonylureas were administered from diagnosis. Serum creatinine was slightly elevated to 1.9 mg/dl. Serum IgA was elevated to 400 mg/dl and electrophoresis revealed the presence of monoclonal IgA λ . Histological analysis of bone marrow specimens showed diffuse expansion of 4 % abnormal plasma cells. To clarify the aetiology of renal lesions, we performed renal biopsy, which revealed diffuse or nodular (Kimmelstiel–Wilson) glomerulosclerosis without amyloid deposition and cast nephropathy that is compatible with advanced diabetic nephropathy (Fig. 1a). At this point, the exact degree of light chain deposition in glomerular lesions was not clear because there was no examination by immunofluorescence studies for IgG, A, λ and C3. We made a diagnosis of diabetic nephropathy complicated with monoclonal gammopathy of undetermined significance (MGUS). Despite the effort to control his DM, renal insufficiency became worse and the IgA serum level increased. To determine the relationship between his MGUS and renal insufficiency, he was admitted to our institution on 16 December 2010.

On admission, the patient was normotensive (blood pressure, 140/68 mm Hg; heart rate, 66 beats/min). Physical examination revealed lower-extremity oedema. The laboratory findings are summarised in Table 1. Serum IgA and β 2-microglobulin were elevated to 1200 mg/dl and 18.2 mg/l, respectively. Moreover, electrophoresis revealed the presence of monoclonal IgA λ . A bone scintigraphy scan showed the uptake in the thoracic vertebrae and ilia (Fig. 1b). Histological analysis of bone marrow

specimens showed diffuse expansion of 12 % abnormal plasma cells (Fig. 1c). In the flow cytometric analysis of bone marrow specimens, the surface marker was positive for CD19, CD38, CD138 and λ chain.

On the basis of all these findings, we gave a final diagnosis of IgA-type MM (Durie–Salmon stage IIIB) derived from MGUS. The patient was classified as ‘high risk’ according to the international scoring system for MM on the basis of the following findings: serum β 2-microglobulin >5.5 mg/l (Table 2) [4–6]. To control his back pain due to iliac lesions, we performed radiation therapy at a dose of 30 Gy. Next, we performed systemic chemotherapy. Before chemotherapy, haemodialysis was initiated because of his ESRD and the high risk of development with tumour lysis syndrome [10, 11]. First, we administered bortezomib (1.0 mg/body) and dexamethasone (20 mg/body) weekly (Fig. 2). During the first course of chemotherapy, tumour lysis syndrome was well controlled at low blood levels of uric acid under the administration of haemodialysis and rasburicase. However, after 2 courses of these therapies, his renal dysfunction worsened (Cr 13.0 mg/dl) without urination on 13 March 2011, because of uncontrolled MM progression. Moreover, fungal pneumonia was complicated and treated with micafungin during the chemotherapy. Serum IgA was extremely elevated to 2400 mg/dl. Because his renal function cannot be controlled, we established a blood access site for permanent haemodialysis. His performance status declined to 3, owing to the activity of MM. Subsequently, we administered an adjusted dose of lenalidomide (5 mg, 3 times/week, after haemodialysis) to control the activity of MM because approximately two-thirds of the lenalidomide is eliminated by haemodialysis [12] (Fig. 2). After undergoing 2 courses of lenalidomide with haemodialysis, he attained partial response (PR) with a lowering of creatinine and IgA levels. After the administration of chemotherapy, he was again

Fig. 1 **a** Renal biopsy showing diffuse or nodular (Kimmelstiel–Wilson) glomerulosclerosis without amyloid deposition and cast nephropathy that is compatible with advanced diabetic nephropathy. At this point, the exact degree of light chain deposition in glomerular lesions was not clear because there was no examination by

immunofluorescence studies for IgG, A, λ and C3. **b** Bone scintigraphy FDG-PET/CT scan showing multiple bone lesions in the ilia, ribs and thoracic vertebrae. **c** Histological findings showing diffuse expansion and infiltration of abnormal plasma cells

Table 1 Laboratory findings on admission

Urinalysis		Coagulation		Serology	
Protein	+++	PT (s)	12.4 s	CRP	0.7 mg/dl
Sugar	+	APTT (s)	36.2 s	HTLV-I	Negative
Occult blood	+	Fib	256.2 mg/dl	HbA1C	6.4 %
Urine sediment		FDP	1.6 mg/dl	IgA	1200 mg/dl
Erythrocytes	10/high-power field	Serum chemistry		β2-microglobulin	18.2 mg/l
Urinary protein	3.1 g/day				
Peripheral cell count		T.Bil	0.21 mg/dl		
WBC	$3.3 \times 10^3/\mu\text{l}$	AST	30 IU/l		
STAB	0.0	ALT	37 IU/l		
SEG	74.0 %	LDH	250 IU/l		
LYMPH	15.0 %	γ-GTP	15 IU/l		
MONO	4.0 %	Na	138 mEq/dl		
EOSIN	5.0 %	Glu	143 mg/dl		
BASO	0.0 %	K	4.19 mEq/dl		
RBC	$22 \times 10^4/\mu\text{l}$	Cl	100 mEq/dl		
Hb	7.1 g/dl	Ca	8.0 mg/dl		
Hct	20.6 %	BUN	88.4 mg/dl		
MCV	93.2 fl	CRE	7.4 mg/dl		
MCH	32.1 pg	UA	9.8 mg/dl		
PLT	$16.0 \times 10^4/\mu\text{l}$	Ferritin	176 ng/ml		
Ret	0.6 %	TP	7.3 g/dl		
		ALB	2.8 g/dl		

WBC white blood cell count, RBC red blood cell count, Hb haemoglobin, MCV mean corpuscular volume, MCH mean corpuscular haemoglobin concentration, PLT platelet count, PT prothrombin time, APTT activated partial thromboplastin time, Fib Fibrinogen, FDP fibrin/fibrinogen degradation products, T.Bil total bilirubin, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, γ-GTP gamma-glutamyl transpeptidase, BUN blood urea nitrogen, CRE creatinine, TP total protein, ALB albumin, CRP C-reactive protein, HTLV-I human T cell leukemia virus type I, HbA1C haemoglobin A1c

Table 2 The International Staging System (ISS) for myeloma was published by the International Myeloma Working Group

Stage	β2M and albumin levels
Stage I	β ₂ -microglobulin (β2M) <3.5 mg/l and albumin ≥3.5 g/dl
Stage II	β2M <3.5 mg/l and albumin <3.5 g/dl or β2M 3.5–5.5 mg/l irrespective of the serum albumin
Stage III	β2M ≥5.5 mg/l

able to urinate with haemodialysis. However, a thrombocytopaenia developed during chemotherapy. Red blood cell concentrate (RCC) transfusions became necessary during the 2 courses of lenalidomide therapy because of the myelosuppression of proliferation of plasma cells, lenalidomide and haemodialysis, which can cause blood spoiling at every session. After 3 courses of lenalidomide therapy, RCC transfusions became no longer necessary. He showed improvement in performance status from 3 to 0 through these treatments and rehabilitation. Subsequently, we performed 8 courses of lenalidomide therapy in the adjusted dose manner. Consequently, these treatments led the patient to be PR that is defined as >50 % reduction in the

level of the serum monoclonal paraprotein over 6 weeks according to the criteria of MM [12]. Although the monitoring of free light chains analysis was useful for evaluating the efficacy of treatments, the free light chains analysis was not performed because there was no availability of commercial-based free light chains examinations.

A major concern with lenalidomide therapy is the risk of severe thrombosis, bacterial and fungal infection, thrombocytopaenia and the development of a secondary malignancy. However, no major adverse events except thrombocytopaenia were seen in our case.

Consequently, after 8 courses of lenalidomide therapy, the patient maintained PR and did not require further RCC transfusion for MM for 21 months.

Discussion

For the primary disease of the new patients begun on haemodialysis, the percentages of patients with diabetic nephropathy and MM were 43.4 % (16053 patients among 37019 patients) and 0.4 % (159 patients among 37019 patients), respectively [1]. Maisonneuve et al. reported that

Fig. 2 Clinical course of our patient. The case developed IgA-type multiple myeloma (MM; Durie–Salmon stage IIIB) derived from monoclonal gammopathy of undetermined significance concomitant with ESRD due to diabetic nephropathy. First, haemodialysis was initiated before chemotherapy, and bortezomib and dexamethasone were found to be ineffective. Subsequently, 8 courses of dose-adjusted lenalidomide therapy were administered according to the degree of haematological and renal functions. The patient remained in partial remission without disease progression for 21 months

the incidence of MM in patients undergoing dialysis was 3–5 times higher than that in healthy people [13]. However, it is not clear as to whether haemodialysis itself increases the risk of malignancy [1, 13, 14]. The development of new agents such as bortezomib, lenalidomide or thalidomide as first-line treatments for MM has led to the improvement in the prognosis of MM patients to beyond 5 years [2–4]. However, the results of treatment of MM with renal insufficiency have been poor [15, 16]. At diagnosis, the serum creatinine value is increased in almost 50 % of all MM patients and is >2 mg/dl in 20 % [2–4]. Therefore, the strategy of using bortezomib, lenalidomide or thalidomide is crucial for improving the poor outcome of MM with renal insufficiency.

In our case, the primary disease begun on haemodialysis was diabetic nephropathy. Subsequently, disease progression from MGUS to MM occurred during the immunosuppressive state of ESRD. Consequently, renal dysfunction based on diabetic nephropathy may be made worse by the additional disease progression of MM.

To the best of our knowledge, this is the first report of a patient who received dose-adjusted lenalidomide therapy for bortezomib-resistant MM concomitant with ESRD due to diabetic nephropathy requiring haemodialysis, wherein haemodialysis was initiated at disease progression from MGUS to MM. Our findings show that adjusting the drug dose and modifying the therapy according to the degree of haematological and renal dysfunction, and according to complications, is a safe, efficient and feasible treatment strategy.

To date, ESRD patients undergoing haemodialysis have not been successfully treated for MM because of the

insufficiency in the drug dose caused by renal dysfunction and because of the risk of infection under immunocompetent conditions [17]. The appropriate dosage, combination and course of therapeutic agents for MM concomitant with ESRD requiring haemodialysis have not yet been established. According to previous reports, bortezomib and dexamethasone are administered first, and in refractory cases, subsequent treatments with lenalidomide and dexamethasone are then performed [7–9]. Bortezomib is not filtered by the kidney and, therefore, does not need to be dose-adjusted according to the degree of renal function [16, 18]. In previous studies, bortezomib treatment improved survival in one-third of MM patients with renal insufficiency [16, 18]. However, in two-thirds of bortezomib-refractory MM patients with renal insufficiency, subsequent treatment was necessary to improve renal insufficiency [16, 18]. To date, few previous studies (<20 cases) have reported the successful treatment of MM concomitant with ESRD requiring haemodialysis by using lenalidomide [7–9] (Table 3). In ESRD patients, treatment with a dose-adjusted lenalidomide therapy (e.g. 5 mg/day, 3 times/week or 15 mg/day, 3 times/week) was found to be effective [7–9, 19, 20]. Lenalidomide is eliminated by up to ~80 % due to haemodialysis [19]. In our case, we modified the dosage of lenalidomide to 5 mg/day, 3 times/week, without dexamethasone after haemodialysis because of the fungal infection during the prior bortezomib and dexamethasone therapy, and also because of the patient's DM and ESRD. During chemotherapy, thrombocytopenia was the only complication observed in our patient. He was administered 6 courses of lenalidomide to achieve a good

Table 3 Lenalidomide therapy in multiple myeloma on haemodialysis

References	No. of patients on haemodialysis	Presence of diabetic nephropathy	Presence of MGUS	Prior treatment	Lenalidomide treatment	Change of CR	No. of patients with response	Outcome
de la Rubia et al. [7]	15	n.d.	n.d.	Bortezomib or thalidomide	Dose-adjusted lenalidomide	n.d.	60 % (PR)	Median OS: 20 months
Dimopoulos et al. [8]	1	n.d.	n.d.	n.d.	Lenalidomide 15 mg, 3 times/week	n.d.	n.d.	n.d.
Klein et al. [9]	4	n.d.	n.d.	n.d.	Lenalidomide 15 mg, every other day after haemodialysis	n.d.	n.d.	n.d.
Present case	1	Diabetic nephropathy	MGUS	Bortezomib and dexamethasone (2 courses)	Lenalidomide 5 mg, 3 times/week (6 courses)	13 → 6	1	Alive (16 months)

Previously published reports on multiple myeloma patients and the present patient in whom lenalidomide therapy was performed

PR partial response, n.d. not described, CR complete remission

outcome. Although a major concern with lenalidomide is the risk of severe thrombosis, bacterial and fungal infection, thrombocytopaenia and the development of secondary malignancy [2–6], no major adverse events, except thrombocytopaenia, were observed in our case.

In conclusion, our findings suggested that dose-adjusted lenalidomide along with haemodialysis is effective for treating bortezomib-refractory MM concomitant with ESRD. A randomised prospective study on patients undergoing haemodialysis is required in order to further understand the incidence, indications for treatment, therapeutic strategy, and dosage and courses of chemotherapy for MM in ESRD patients undergoing haemodialysis.

Conflict of interest Noriaki Kawano and the other co-authors have no conflict of interest.

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