

[CASE REPORT]

Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Associated with Nephrotic Syndrome during Hemodialysis, Treated Successfully with Tirabrutinib

Yasunobu Sekiguchi¹, You Nishimura², Hiroaki Kanda², Machiko Kawamura³,
Kazuhiko Kobayashi³ and Hirofumi Kobayashi¹

Abstract:

A 74-year-old woman was diagnosed with Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) in X-18. Fludarabine plus rituximab (FR) was started, and she showed remission. In July X-7, the serum creatinine (Cr) level increased to 1.67 mg/dL, and bendamustine plus rituximab (BR) was started. By November X-7, the Cr level had increased to 8.41 mg/dL, so she was started on hemodialysis (HD). In September X-1, she developed nephrotic syndrome. She was started on tirabrutinib at 480 mg. In July X, her nephrotic syndrome had improved, and a complete response (CR) was achieved. This is the first case of the administration of tirabrutinib in a patient undergoing HD.

Key words: Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL), tirabrutinib, chronic renal failure, nephrotic syndrome, hemodialysis

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Introduction

Tirabrutinib is a second-generation inhibitor of Bruton tyrosine kinase (BTK) and has been found to have fewer off-target effects than the first-generation inhibitors (1-4). Clinical studies have also reported fewer adverse events and a higher response rate to tirabrutinib (3-6). However, use of this drug in clinical practice has not yet been reported.

Japan is the only country in the world in which tirabrutinib has been launched in the market, allowing the drug to be used in clinical practice. At present, a number of clinical studies are ongoing overseas (6), and tirabrutinib is expected to be launched in the market outside of Japan in the near future. Therefore, it is important to report experience of using tirabrutinib in clinical practice in Japan.

We herein report a patient with Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL)-related renal dysfunction and nephrotic syndrome who was successfully treated with tirabrutinib in combination with hemo-

dialysis (HD).

Case Report

A 74-year-old woman with no significant medical or family history developed left mandibular swelling and low back pain in X-19. Her subsequent clinical course is shown in Fig. 1.

In November X-18, she visited our hospital (Fig. 1A). Table shows the laboratory findings at her first visit. An examination of a peripheral blood smear revealed the presence of 3% atypical lymphocytes. The plasma soluble interleukin-2 (IL-2) receptor level was 3,725 international units (IU)/ μ L, and the plasma IgM level was 2,565 mg/dL. Serum immunoelectrophoresis revealed a positive result for IgM- κ . She was found to have a gingival tumor in the left mandible, and a biopsy was performed. A histopathological examination of sections stained with hematoxylin and eosin (H&E) revealed proliferation of atypical plasmacytoid lymphocytes (Fig. 2A). On immunohistochemistry, the cells showed posi-

¹Department of Hematology, Saitama Cancer Center, Japan, ²Department of Pathology, Saitama Cancer Center, Japan and ³Department of Clinical Laboratory Medicine, Saitama Cancer Center, Japan

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Correspondence to Dr. Yasunobu Sekiguchi, yasu_sek@saitama-pho.jp

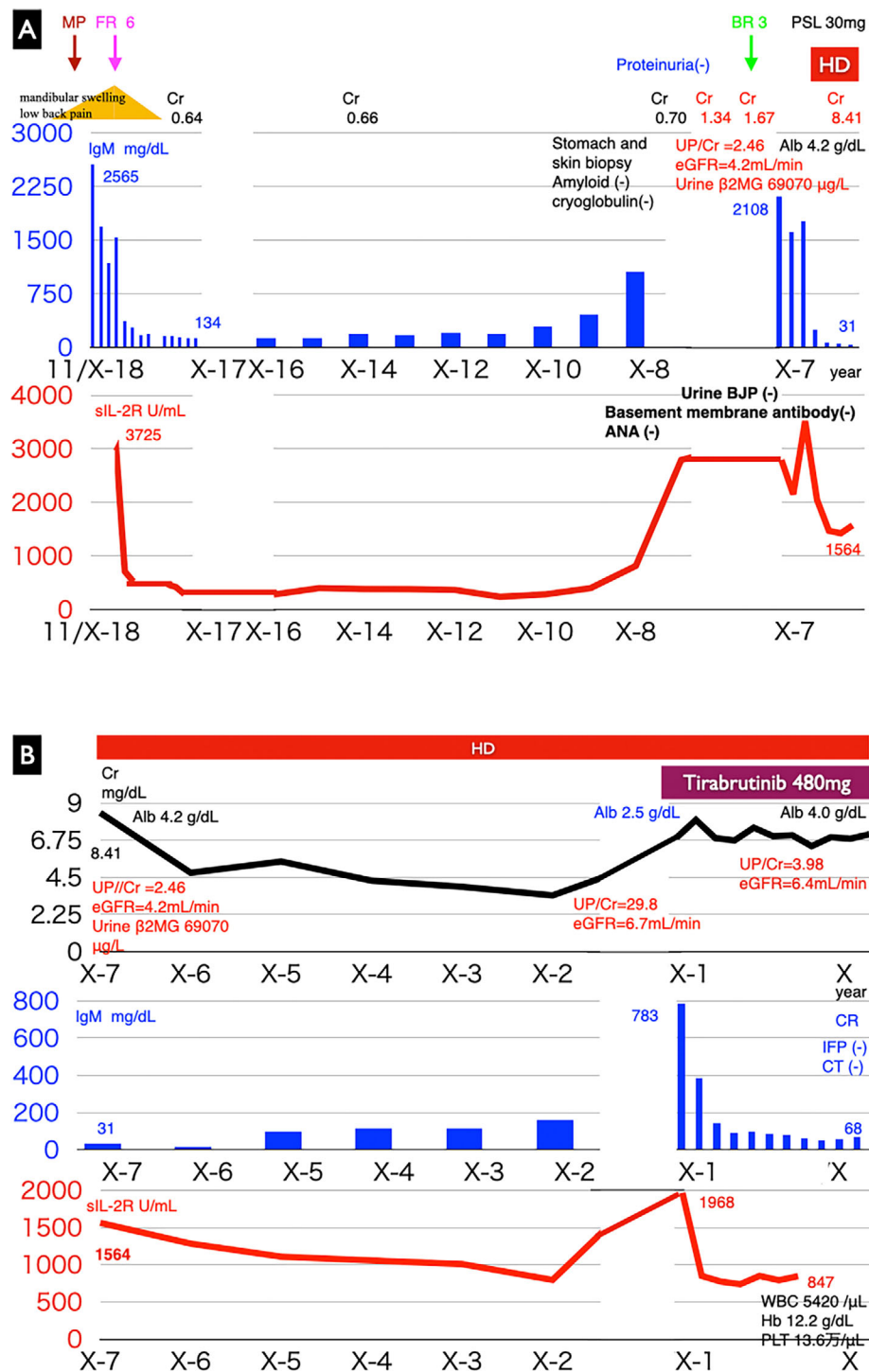


Figure 1. Clinical course. **A:** From the onset to the initiation of HD. **B:** From the initiation of HD to the present. MP: melphalan, prednisolone, FR: fludarabine, rituximab, sIL-2R: soluble IL-2 receptor, BUN: blood urea nitrogen, Cr: creatinine, BR: bendamustine, rituximab, UP: urine protein, eGFR: estimated glomerular filtration rate, min: minute, MG: microglobulin, BJP: Bence-Jones protein, PSL: prednisolone, HD: hemodialysis, Alb: albumin, CR: complete remission, IFP: immunofixation method, WBC: white blood cells, Hb: hemoglobin, PLT: platelet

tive staining for CD 20, CD138, immunoglobulin M (IgM), and κ chain and negative staining for λ chain (Fig. 2B-F). Based on the above findings, she was diagnosed with LPL.

Computed tomography (CT) revealed multiple lymphadenopathies and hepatosplenomegaly (data not shown). Magnetic resonance imaging (MRI) revealed multiple bone le-

sions (data not shown). A bone marrow examination showed an increase in medium-sized lymphocytes (26.4%) with nuclear atypia (Fig. 2G, H). Among cell surface markers, the cells were positive for CD20 (data not shown). Based on these findings, she was diagnosed with WM/LPL (7). The test for an MYD88 mutation in a specimen of bone marrow

Table. Laboratory Findings at the First Visit to Our Hospital.

CBC		Biochemistry		Immuno-Serological findings	
WBC	9,330 / μ L	T.P	8.8 g/dL	HTVL-1 Ab	negative
Seg	56.0 %	Alb	4.0 g/dL	HIV Ab	negative
Eo	1.0 %	BUN	11 mg/dL	HBsAg	negative
Ba	1.0 %	Cr	0.57 mg/dL	HBsAb	negative
Mono	5.0 %	T-B	il 1.1	HBcAb	negative
Lympho	34.0 %	AST	13 IU/L	HCVAb	negative
Aty Lym	3.0 %	ALT	4 IU/L	IgG	1,027 mg/dL
RBC	313 \times 10 ⁴ / μ L	LDH	119 IU/L	IgA	49 mg/dL
Hb	10.2 g/dL	ALP	516 IU/L	IgM	2,565 mg/dL
Hct	31.9 %	AMY	40 IU/L	ANA	<40 times
MCV	102 fL	γ -GTP	13 IU/L	Serum IEP IgM- κ	
MCH	32.5 pg	T-CHO	200 mg/dL		
		BS	89 mg/dL		
		CRP	2.9 mg/dL		

WBC: white blood cells, Seg: segmented, Eo: eosinophil, Ba: basophil, Mono: monocyte, Lympho: lymphocyte, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, T.P: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatine, T-BIL: total-bilirubin, AST: aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, AMY: amylase, γ -GTP: γ -guanosine triphosphate, T-CHO: total cholesterol, BS: blood sugar, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor, HTLV-1 Ab: human T-cell leukemia virus type 1 antibody, HIV Ab: human immunodeficiency virus antibody, HBsAg: hepatitis B virus antigen, HBsAb: hepatitis B virus antibody, HBcAb: hepatitis B virus core antibody, HCV Ab: hepatitis C virus antibody, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, ANA: antinuclear antibody, IEP: immunoelectrophoresis

aspirate was negative.

She was assessed as having a low risk according to the International Prognostic Scoring System for Waldenstrom Macroglobulinemia (ISSWM) (8). She complained of severe low back pain and was started on melphalan plus prednisolone (MP) therapy. However, the effect was only transient, and the treatment was switched to fludarabine plus rituximab (FR) therapy. The low back pain resolved, and the plasma M protein level decreased in response to this treatment. She was administered six courses of chemotherapy and subsequently followed up.

The plasma M protein level began to increase gradually from X-10, and evidence of renal function impairment was detected in April X-7 [creatinine (Cr), 1.34 mg/dL]. She was diagnosed with renal dysfunction caused by WM/LPL (WM/LPL-related renal dysfunction).

In July X-7, the Cr increased to 1.67 mg/dL, and she was started on bendamustine plus rituximab (BR) therapy. Although the plasma M protein level decreased, the renal impairment worsened rapidly. She was started on 30 mg/day of prednisolone, but the renal parameters failed to improve. By November X-7, the Cr level had increased to 8.41 mg/dL, and she was started on maintenance HD (3 days a week: Mondays, Wednesdays, and Fridays). The urinary protein/Cr ratio was 2.46. The serum albumin level (Alb) was 4.2 g/dL. She did not consent to undergo a renal biopsy. The qualitative test for cryoglobulin was negative. Stomach and skin biopsies revealed no evidence of amyloid depositions. The urinary test for Bence-Jones protein was negative. Basement membrane antibody was negative.

The plasma M protein level increased gradually. In September X-1, the serum Alb decreased to 2.5 g/dL and the urinary protein/Cr ratio increased to 29.8 (Fig. 1B). She was diagnosed with nephrotic syndrome (9). CT revealed multiple superficial lymphadenopathies but no hepatosplenomegaly or bone lesions (data not shown).

She was started on tirabrutinib at 480 mg once daily. On the scheduled HD days, tirabrutinib was administered after the HD session, as the drug removal rate of tirabrutinib during HD is still unknown. The plasma M protein level decreased. In July X, the Alb level increased to 4.0 g/dL and the urinary protein/Cr ratio improved to 3.98. Immunofixation electrophoresis (IFP) yielded negative findings, and CT no longer showed lymphadenopathy or hepatosplenomegaly. A bone marrow examination also revealed no abnormalities, and she was determined to have shown a complete response (CR) (10). At present, in October X, she continues to receive tirabrutinib and has developed no adverse events (AEs).

Discussion

According to reports, MYD88 mutations are seen in 70-90% of patients with WM/LPL, but some patients with WM/LPL are negative for MYD88 mutations (11). Thus, the absence of MYD88 mutations does not necessarily exclude WM/LPL. Furthermore, 37.1% of Japanese patients with WM/LPL are reported to have bone lesions (11), so the presence of bone lesions cannot serve as a basis for excluding WM/LPL. A biopsy of the gingival tumor and examina-

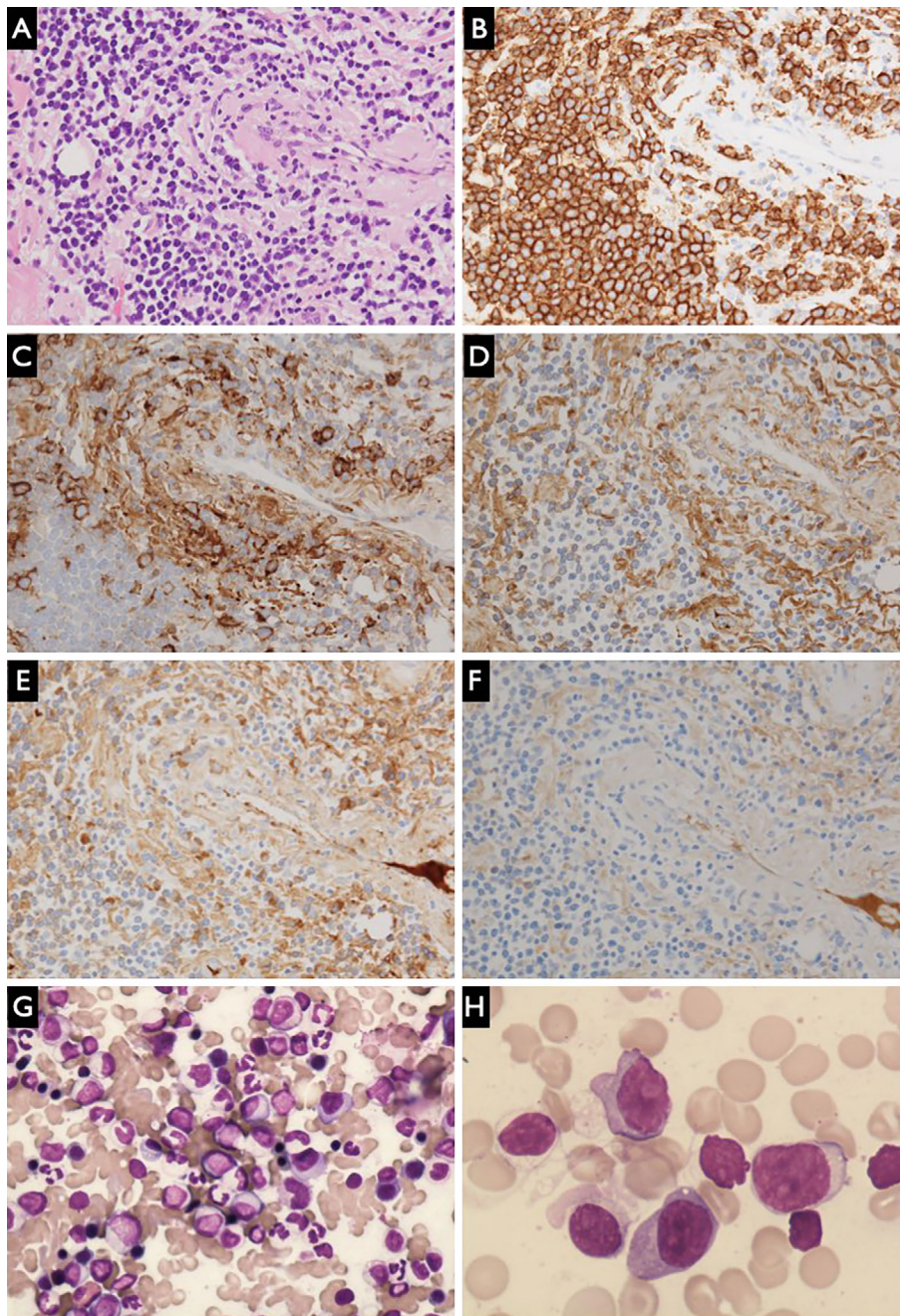


Figure 2. A-F: Biopsy of the gingival tumor, G, H: Bone marrow. A: Hematoxylin and Eosin staining $\times 40$; Proliferation of atypical plasmacytoid lymphocytes is observed. B: CD20 $\times 40$; positive. C: CD138 $\times 40$; positive. D: IgM $\times 40$; positive. E: $\kappa \times 40$; positive. F: $\lambda \times 40$; negative. G: Smear $\times 400$; Medium-sized lymphocytes with nuclear atypia increased. H: Smear $\times 1,000$; Medium-sized lymphocytes with nuclear atypia increased.

tion of the bone marrow aspirate revealed atypical plasmacytoid lymphocytes that were CD20-positive. Based on the above findings, multiple myeloma was excluded, and the patient was diagnosed with WM/LPL.

Tirabrutinib has yet to be launched in markets outside of Japan, and major overseas guidelines [National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines] do not cover tirabrutinib (12, 13). The Japanese Society of Hematology guidelines also do not cover it, as they have not been revised

since the date of approval of this new drug (August 21, 2020) (14). The optimal clinical indications and timing for treatment with tirabrutinib in clinical practice are still unknown. In addition, whether or not tirabrutinib is effective in patients with WM-related renal failure or nephrotic syndrome is also still unknown, as is the drug's effect in patients on HD. It would be desirable to accumulate experience and establish evidence concerning the safety and efficacy of tirabrutinib in clinical practice in Japan.

Thile the first-generation BTK inhibitor ibrutinib is

known to show scarce renal excretion (15), its pharmacokinetics and pharmacodynamics in HD patients remain unknown (15). The drug removal rate of ibrutinib through HD also unknown. Only two cases of ibrutinib use in HD patients have been reported (15, 16). In one case, a patient with chronic lymphocytic leukemia received ibrutinib for two weeks, and HD was able to be suspended (16). In the other case, a patient with mantle cell lymphoma continued to receive ibrutinib for 15 months (15). There were no serious AEs in either case, and ibrutinib was effective, suggesting that ibrutinib is also safe and effective in patients undergoing HD, although further evidence is still needed (15, 16).

In cases of WM associated with renal failure, it is necessary to differentiate between WM-related renal failure and other causes of renal failure (e.g. diabetes mellitus, hypertension, malignant tumors, and drug-induced) (17). The present patient was considered to have WM-related renal dysfunction, because the renal function worsened in parallel with the progression of WM/LPL (increase of the plasma levels of M protein and soluble IL-2 receptor) (Fig. 1B), and there was no evidence of other causes of renal failure mentioned above.

WM-related renal failure is relatively rare, with a cumulative incidence of 5.1% at 15 years, and carries a poor prognosis (17). There are a number of mechanisms underlying the development of the failure, including amyloidosis, IgM deposition/cryoglobulinemia, LPL infiltration, light chain deposition, and light chain cast nephropathy (17, 18). A renal biopsy is required to determine the precise cause (17, 18).

WM-related renal failure sometimes progresses to a stage requiring renal replacement therapy (RRT) (17, 19). After progression to the stage of nephrotic syndrome, conservative treatment has been reported to be effective in only half of patients (17). WM-related renal failure has a poor prognosis (17) and needs appropriate treatment; however, the optimal treatment is still unknown (20). In addition, it has been reported that a decrease in the plasma M protein level (hematologic response) is not always directly related to improvement of the renal function (19, 21). Caution should be exercised in its treatment. In fact, in the present case, BR therapy decreased the plasma M protein level but did not improve the renal function, necessitating the initiation of maintenance HD (Fig. 1A). When these patients begin to show evidence of renal impairment, early and appropriate treatment is necessary (17).

In the present case, stomach and skin biopsies revealed no evidence of amyloid deposition, and the qualitative test for serum cryoglobulin was negative (Fig. 1A). We believe that amyloidosis and IgM/cryoglobulin deposition were unlikely. In three previous cases of WM/LPL, treatment elicited a hematologic response, but HD could not be discontinued (19, 21). A histopathological examination of the kidney in these three cases revealed rapidly progressive glomerulonephritis (RPGN) in one case, cast nephropathy in one case, and light-chain deposition disease (LCDD) in one

case. It is suspected that these lesions were irreversible. The renal lesion in the present case was also irreversible, suggesting that the findings probably corresponded to one of the above diseases.

There have been no reports of tirabrutinib administration in patients with severe renal failure [estimated glomerular filtration rate (eGFR) of ≤ 30] or those on maintenance HD (these patients have been excluded from clinical studies so far) (4, 5, 22-24). Therefore, the efficacy and safety of the drug in these patients are unknown. In addition, the removal rate of this drug by HD is also unknown (21). Since unchanged tirabrutinib was not detected in the urine (25), it is presumed that the drug is metabolized in the liver. Theoretically, tirabrutinib can be administered to patients with renal failure. However, whether or not its removal by HD might also reduce its efficacy is unknown.

In the present case, the nephrotic syndrome (WM/LPL-related renal dysfunction) improved (urinary protein/Cr ratio decreased from 29.8 to 3.98 and serum Alb level increased from 2.5 g/dL to 4.0 g/dL), and CR of WM/LPL was achieved (Fig. 1E). No AEs were observed. The results suggest that tirabrutinib is effective and safe in patients with WM/LPL-related renal failure on HD.

Several limitations associated with the present study warrant mention. First, we did not perform a renal biopsy and thus could not examine the renal lesion in detail. Second, treatment with tirabrutinib was started six years after the initiation of HD, and it is considered difficult to withdraw a patient from HD even after improvement of nephrotic syndrome. Third, the follow-up period was short at approximately one year.

In conclusion, we encountered a patient who was treated on tirabrutinib while undergoing maintenance HD. The nephrotic syndrome was successfully controlled by tirabrutinib, and CR of WM/LPL was achieved. Although the results suggest that tirabrutinib may be useful in WM/LPL patients undergoing maintenance HD, the further accumulation of cases and longer-term follow-up are necessary.

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

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