Zanubrutinib, rituximab and lenalidomide induces deep and durable remission in *TP53*-mutated B-cell prolymphocytic leukemia: a case report and literature review

B-cell prolymphocytic leukemia (B-PLL) is a rare lymphoid neoplasm accounting for approximately 1% of all cases of lymphocytic leukemia. In this disease, *TP53* abnormalities are found in more than half of the cases and about 50% of patients have *MYC* abnormalities (rearrangement and/or increased copy number). Similar to chronic lymphocytic leukemia (CLL), shortened survival in B-PLL is associated with *TP53* mutations. Due to the rarity of this disease, most therapeutic approaches have been executed according to CLL guidelines. Specifically, Bruton's tyrosine kinase (BTK) inhibitors show significant efficacy in CLL patients with 17p deletion/*TP53* mutation. However, little is known about the treatment outcome of BTK inhibitors (BTKi) in B-PLL. Here, we report for the first time the efficacy of a next-generation BTKi, zanubrutinib, combined with rituximab and lenalidomide (ZR2), in a B-PLL patient with *TP53* and MYC abnormalities.

A 52-year-old man visited our hospital in October 2020 with a 3-year history of high white blood cell (WBC) count and splenomegaly. Physical examination revealed multiple palpable lymphadenopathies (bilateral neck, bilateral supraclavicular, bilateral axillary, and bilateral inguinal regions) and massive splenomegaly (19 cm below left costal margin). Complete blood count showed an elevated WBC count of 31.4×10^9/L, hemoglobin concentration of 134 g/L and platelet count of 87×10^9/L. Peripheral blood (PB) smear revealed 88% of prolymphocytes. Serum lactate dehydrogenase (313 U/L, normal <250 U/L) and β2-microgloubulin (5.42 mg/L, normal <2.8 mg/L) were elevated. The concentration of serum monoclonal immunoglobulin G (IgG) with λ light chain, detected by immunofixation electrophoresis, was 2.8 g/L. Abdominal ultrasound showed splenomegaly (24.6×8.2 cm, 19 cm below left costal margin). 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) scan showed slightly increased FDG metabolism of lymph nodes in the neck, axilla, mediastinum, retroperitoneum, abdominal cavity, pelvic cavity, and groin (the largest diameter is 1.5 cm, SUV_{max} 4.3). It also demonstrated increased FDG metabolism of spleen (SUV_{max} 4.3). A bone marrow (BM) biopsy showed B-PLL representing 75% of the marrow cells. Flow cytometry showed these cells were positive for CD19, CD79a, FMC7, CD81, CD22, CD20, and restricted monoclonal λ light chain, together with weakly positive for CD23, CD25, CD38, CD200, surface immunoglobulin M (sIgM), and negative for CD5, CD10, CD43, CD71, CD123, CD103, CD11c, surface IgD (sIgD) and κ light chain. These cells were stained negative for cyclin D1. Immunoglobulin heavy chain (IGH) somatic hypermutation analysis showed mutated IGH variable region genes. Cytogenetics revealed t(8;14) and fluorescense *in situ* hybridization (FISH) showed *MYC* gene rearrangement without *CCND1/IgH* rearrangement which exclude the diagnosis of mantle cell lymphoma (MCL). Molecular studies showed mutations in both *MYC* and *TP53* genes. Based on cell morphology, histopathology, immunohistochemistry, genetic analysis, and clinical features, the patient was diagnosed as B-PLL.

This patient was treated with ZR2 regimen (zanubrutinib, 160 mg twice daily on day 1-21; lenalidomide, 25 mg once daily on day 1-14; rituximab, 375 mg/m^2 on day 1) every 28 days. Following the initiation of ZR2 treatment, the patient experienced resolution of splenomegaly, with the WBC decreasing from 31.4×10^9/L to 8.43×10^9/L after one cycle treatment (Table 1). Minimal residual disease (MRD) negative complete remission (CR) (by PB flow cytometry and PET-CT scan) was achieved after four cycles of ZR2 treatment, with monoclonal IgG disappearance. The patient refused allogeneic hematopoietic stem cell transplantation (HSCT). After 6 cycles of ZR2 treatment, MRD negative CR was further verified by PET-CT and flow cytometric analysis of bone marrow aspirates. Subsequently, the patient received two cycles of ZR (zanubrutinib, 160 mg twice daily on day 1-21; rituximab, 375 mg/m^2 on day 1) as consolidation therapy. Thereafter, zanubrutinib and lenalidomide (zanubrutinib, 160 mg twice; lenalidomide, 25 mg once daily on day 1-14; administered every 28 days) were used as maintenance therapy. Moreover, the patient has been well and has remained in sustained MRD-negative CR for 12 months by now. The most hematological adverse events were common grade 1-2 neutrophil count decrease, which can be recovered in a few days, and no significant non-hematological adverse events such as nausea and fatigue were noted.

There are an estimated 120 new cases of B-PLL per year in the United States and prospective clinical trials are currently not available. There is neither clear expert consensus nor are there guidelines for the treatment of B-PLL, and the treatment according to CLL are frequently recommended as upfront therapy. In patients with *TP53* mutation and/or deletion, alemtuzumab was an effective

Table 1. Treatment course.

Time point		Response evaluation					
		WBC count (x10^9/L)	ALC (x10^9/L)	LDH (U/L)	PET/CT	PB MRD	BM MRD
Baseline		31.4	27.6	313	Spleen, lymph node	88%	75%
Cycle 1	ZR2	8.43	5.10	245	N/A	N/A	N/A
Cycle 2	ZR2	4.23	2.67	362	N/A	14.26%	N/A
Cycle 3	ZR2	3.52	1.0	255	N/A	NEG	N/A
Cycle 4	ZR2	3.06	1.0	192	CR	NEG	N/A
Cycle 5	ZR2	3.69	1.27	184	N/A	NEG	N/A
Cycle 6	ZR2	3.04	1.29	196	N/A	N/A	NEG
Cycle 7	ZR	4.62	1.59	220	N/A	N/A	N/A
Cycle 8	ZR	2.41	0.83	206	N/A	NEG	N/A

WBC: white blood cell count; ALC: absolute lymphocyte count; LDH: lactate dehydrogenase; PB: peripheral blood; BM: bone marrow; MRD: measurable residual disease; N/A: not available; NEG: negative; CR: complete remission; ZR2: zanubrutinib+lenalidomide+rituximab; ZR: zanubrutinib+rituximab.

Table 2. **Ibrutinib treatment in patients with B-cell prolymphocytic leukemia.**

	Reference	N	Age, years	Cytogenetics	Treatment	Outcome	Ibrutinib treatment-related adverse events	Response criteria
Ibrutinib monotherapy	Gordon *et al.*, 2017[2]	2	73, 77	del(17p) del(13q)	Patient 1: single dose R, Ibrutinib started on day 40 Patient 2: single dose BR, Ibrutinib started on day 44	Patient 1: CCR, PFS: 15 months Patient 2: CCR, PFS: 12 months	1. Mild fatigue and easy bruising, 2. Atrial fibrillation	iwCLL
	Algrin *et al.*, 2017[3]	4	NA	del(17p)	Ibrutinib monotherapy	3CR/1PR, Median PFS: 9 months	-	iwCLL
	Coelho *et al.*, 2017[4]	1	48	del(17p), del(11q), del(13q), trisomy 12, t(11; 14)	1. Idelalisib-rituximab for 5 months 2. Ibrutinib for 2 months 3. Allo-HSCT (reduced intensity)	After allo-HSCT: CR, PFS: 10 months	Transient lymphocytosis	Author's report
	Damlaj *et al.*, 2018[5]	1	67	*MYC* rearrangement	Ibrutinib monotherapy	PFS: 8 months	Easy cutaneous bruising, transient lymphocytosis	Author's report
	Bindra *et al.*, 2019[6]	1	84	del(17p), del(13q)	1. Ibrutinib for 12 months 2. Venetoclax and leukapheresis for 5 weeks	1. Response to ibrutinib for 12 months 2. Patient went to hospice care after Venetoclax	-	Author's report
	Patil *et al.*, 2019[7]	1	66	*TP53* deletion	1. Alemtuzumab for 18 months 2. Idelalisib-rituximab for 12 months 3. Ibrutinib for 12 months 4. Venetoclax for 8 months	1. 3rd line Ibrutinib (hematological PR, PFS: 12months) 2. OS: 5 years	Transient lymphocytosis	Author's report
	Christoforidou *et al.*, 2020[8]	1	77	del(17p)	1. BR for 4 months 2. Ibrutinib for 5 months 3. Venetoclax for 6 months 4. Idelalisib-rituximab for 10 months	1. 2nd line Ibrutinib (hematological PR, PFS: 5 months) 2. OS: 2.5 years	Atrial fibrillation, gastric hemorrhage, transient lymphocytosis	Author's report
	George *et al.*, 2020[9]	1	73	t(4;14) (p16.3;q32) , *TP53* mutation	Ibrutinib monotherapy	PR, PFS: 15 months	Transient lymphocytosis	Author's report
	Oka *et al.*,2020[10]	1	71	del(17p)	Low dose Ibrutinib monotherapy	CR, PFS: 12 months	-	Author's report
Ibrutinib combination	Moore *et al.*,2020[11]	6	median age: 67.3 years	*TP53* disruption	IRA(n=2); IR(n=2); Ibrutinib (n=2)	IRA (2 CCR) IR (1 CCR,1 PR) Ibrutinib (1 PR,1 SD) Median PFS: 34.7 months	Recurrent urinary tract infections (1), cutaneous Nocardia infection (1), cytomegalovirus reactivation (1), musculoskeletal pain (3), atrial fibrillation (1), stomatitis requiring dose reduction (1)	iwCLL
	Siddiqui *et al.*,2021[12]	1	68	del(17p), gain *MYC*	1. Ibrutinib for 10 months 2. IR for 3 months 3. IV for 3 years	After IV: CR; Total PFS: 4.5 years	-	iwCLL

R: rituximab; BR: bendamustine + rituximab; IRA: ibrutinib+rituximab+alemtuzumab; IR: ibrutinib+rituximab; I: ibrutinib monotherapy; IV: ibrutinib+venetoclax; iwCLL: international workshop on chronic lymphocytic leukemia; CCR: patients without restaging bone marrow biopsies or imaging, meeting iwCLL clinical and laboratory complete remission criteria were considered to have a clinical complete remission (CCR); PR: partial response; CR: complete response; PFS: progression-free survival; OS: overall survival.

therapeutic option for these patients, despite showing a short reaction time. In a small series of idelalisib plus rituximab in B-PLL, responses were seen in all five patients, which lasts more than 6 months at the time of the report.[1]

BTKi is known to promote high response rates, leading to durable remissions in all genetic subsets of CLL patients including patients with *TP53* abnormalities. As shown in Table 2, ibrutinib has shown efficacy in individual case reports and small case series studies in B-PLL patients.[2-12] Zanubrutinib is a new-generation, irreversible BTKi demonstrating high selectivity and low toxicities. Zanubrutinib has demonstrated single agent safety and efficacy in B-cell malignancies including CLL, lymphocytic lymphoma (LPL) and MCL in several clinical trials. Lenalidomide is an immunomodulatory drug which has direct anti-tumor activity and indirect effects by enhancing anti-tumor immune responses. Lenalidomide can downregulate the expression of MYC and its target genes. Chamuleau *et al.* conducted a prospective R2-CHOP study on newly diagnosed *MYC* rearrangement-positive DLBCL patients which was safe and achieved 67% complete metabolic response.[13] Bühler *et al.* reported that in a study of relapsed/refractory CLL patients treated

with lenalidomide, there was no statistically significant difference in OS between *TP53*-mutant and wild-type patients.[14] Additionally, for CLL patients who have high risk factors including *TP53* mutation, the application of lenalidomide maintenance therapy can bring significant clinical benefits.[15]

Lenalidomide can enhance antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cell-mediated phagocytosis (ADCP) of rituximab, showing rational combination strategy with rituximab. Several studies have shown efficacy and safety of the combination of BTKi (ibrutinib or zanubrutinib) with R2 (lenalidomide and rituximab) and with or without chemotherapy (ibrutinib+R2+CHOP, clinicaltrials gov. Identifier: NCT02077166; ibrutinib+R2, clinicaltrials gov. Identifier: NCT02460276; ZR2+CHOP, clinicaltrials gov. Identifiers: EHA2021 EP548), to treat DLBCL and MCL. In a phase II trial (clinicaltrials gov. Identifier: NCT04460248) previously untreated elderly patients with DLBCL will be treated with ZR2 regimen.

Taken together, lenalidomide showed anti-tumor potential for *MYC* rearrangement-positive DLBCL and *TP53*-mutant CLL, in addition, ibrutinib+R2 showed efficacy for MCL, which may have similar disease characteristics as B-PLL. This patient has both *TP53* and *MYC* mutations along with *MYC* rearrangement, which predicted the poor outcome with short survival period by conventional chemoimmunotherapy. Therefore, we employed ZR2 as a first line therapy for this patient. As far as we know, this is the first case report to document a successful treatment outcome with ZR2 as upfront therapy for a B-PLL patient.

Although effective standard treatment strategies have not yet been established for patients with B-PLL, we here demonstrate that ZR2 regimen induces a deep and durable response in one B-PLL patient with *TP53* and *MYC* mutations along with *MYC* rearrangement. Given the poor prognosis of B-PLL and lack of effective established treatment modalities, this case report could represent a promising indication of ZR2 for B-PLL treatment. Further investigations in large cohort will be needed to characterize the efficacy, safety, and tolerability of this combination treatment.

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