Case Report

B-cell prolymphocytic leukemia with P53 abnormalities successfully treated with bendamustine and rituximab: a report of three cases

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Background: B-cell prolymphocytic leukemia (B-PLL) is a rare mature B-cell tumor with an aggressive clinical course and poor prognosis. It is characterized by prominent splenomegaly and prolymphocytes exceeding 55% of the lymphoid cells in the blood. Purine analog-based chemo-immunotherapy is the first-line therapy for B-PLL. Owing to its rarity, there are few reports on the efficacy of bendamustine and rituximab (BR) regimen. Our study presents three cases of BR being effective in the treatment of B-PLL and provides experience for clinical treatment.

Case Description: This report describes the cases of three male patients (median age: 66 years old) who initially presented with abdominal discomfort. Physical examinations and imaging revealed splenomegaly, while a peripheral blood (PB) smear revealed a prolymphocyte count exceeding 70% of the lymphoid cells. Therefore, the three patients were diagnosed with B-PLL. Further molecular detection showed that they harbored P53 abnormalities (17p deletion/*TP53* mutation) associated with resistance to conventional chemotherapies. In addition, one of the patients had a highly complex karyotype and multiple gene mutations. All patients underwent four cycles of BR, and two of them received two further cycles of rituximab monotherapy. Ultimately, the patients achieved a complete response (CR) that lasted for 25, 33, and 34 months, respectively, with a median follow-up time of 34 months. The adverse events of the BR mainly included a grade 3 haematological toxicities. Also, the treatment was well-tolerated.

Conclusions: This case series suggests that BR regimen is promising for bringing deep remission to patients with B-PLL. Prospective trials are still required for further elucidation.

Keywords: Prolymphocytic leukemia; bendamustine; rituximab; 17p deletion/*TP53* mutation; case report

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Introduction

B-cell prolymphocytic leukemia (B-PLL) is a rare mature B-cell tumor with a poor prognosis, accounting for about 1% of all lymphocytic leukemias (1). This disease primarily occurs in elderly individuals (median age: 69 years) and is slightly more common in males than females (2). Patients with B-PLL are found to have greater than 55% prolymphocytes in the peripheral blood (PB), and typically present with the clinical constellation of spleen-dominant disease, bone marrow involvement, and lymphocytosis (3).

Conventional chemotherapy for B-PLL has low response rates. A retrospective survey revealed that among 29 treated patients, only 1 patient had complete response (CR) and 13 patients had partial response (4). The median overall survival (OS) of B-PLL before rituximab era was only 3–5 years (4,5). At present, purine analog-based chemo-immunotherapy is the first-line therapy for B-PLL. Progression-free survival (PFS) was up to 7 years (6). Bendamustine is a bifunctional alkylating agent with efficacy in many types of lymphoma. Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen on B lymphocytes, has been used widely in the treatment of B-cell non-Hodgkin lymphoma (NHL). However, there are few published reports on rituximab and bendamustine (BR) in the treatment of B-PLL, and its efficacy is unclear. Herein, we review the literature on the role of BR in the treatment of B-PLL and present the cases of three treatment-naïve B-PLL patients who have benefited from a CR to BR. We present this article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-828/rc).

Highlight box

Key findings

- The rituximab and bendamustine (BR) regimen was effective in patients with B-cell prolymphocytic leukemia (B-PLL).

What is known and what is new?

- B-PLL is a rare mature B-cell tumor with an aggressive clinical course and poor prognosis.
- Herein, we presented three treatment-naïve patients with B-PLL who completely responded to the treatment of BR.

What are the implications, and what should change now?

- The results of this study indicate that BR plays a crucial role in B-PLL. Prospective trials are still required for further elucidation.

Case presentation

Three patients visited the First Hospital of Jilin University from August 2019 to December 2019. The patients' baseline characteristics are shown in *Table 1*. All patients were male, with a median age of 66 years old at diagnosis. They complained of abdominal discomfort without previously documented lymphocytosis, and two of them had B symptoms (case 1 with weight loss of >10% within 6 months, case 3 with weight loss of >10% within 6 months and night sweats). Physical examination was only significant for splenomegaly, with the patients' spleens measuring 7.8, 9.2, and 7.2 cm below the costal margin.

Laboratory blood tests revealed that the three patients had an increase in white blood cell (WBC) levels (range, 24.09×10^9–41.33×10^9/L), and one of them had grade-2 normocytic anemia (hemoglobin 9.6 g/dL) with a negative Coombs test. All three PB smears showed a prolymphocyte count greater than 70%. Abdominal ultrasound showed gross splenomegaly (longitudinal diameter: 16.1–17.0 cm). A whole-body positron emission tomography/computer tomography (PET/CT) of two patients showed hypermetabolic lesions in the spleen and extra-nodal sites (bone and liver), as well as simultaneous lymph node involvement in one patient. Morphologically, these round tumor cells (*Figure 1*) were medium to large (i.e., twice the size of normal lymphocytes), in size and had abundant cytoplasm. Furthermore, they also had prominent nucleoli and condensed nuclear chromatin.

Immunohistochemistry displayed co-expression of CD20 by the tumor cells; CD10, CD103, CCND1 (cyclin D1), Sox11, and MUM-1 were not expressed. Flow cytometric analysis revealed that monoclonal B cells expressing mature B-cell antigens (CD19, CD20, CD22, CD79b, FMC7), CD11c, and CD200 exhibited light chain restrictive expression but were negative for CD10, CD103, and CD123. All three patients had a P53 abnormality; a 17p deletion was present in two of the three patients. Mutations in *TP53* (two cases) and *MYD88* (two cases) were also detected. In addition, one patient had a highly complex karyotype (≥ five cytogenetic abnormalities) and multiple gene mutations (*BCOR*, *ETV6*, *KMT2C*, *MYD88*, *TET2*, *TP53*).

As shown in *Figure 2A*, according to previous studies (7,8), all three patients received bendamustine (90 mg/m^2, d1–2) combined with rituximab (375 mg/m^2, d1) every 28 days for up to four treatment cycles. Rituximab was then administered intravenously in two patients at a dose of 375 mg/m^2 every

Table 1 Clinical characteristics and laboratory examinations of three patients

Characteristics	Patient 1	Patient 2	Patient 3
Gender/age, years	M/67	M/49	M/66
Chief complaint	Abdominal fullness and fatigue	An asymptomatic palpable abdominal mass	Abdominal pain
B symptoms	Weight loss of >10% within 6 months	NA	Weight loss of >10% within 6 months and night sweats
Imaging examinations			
Color ultrasound/CT			
Spleen, mm			
Long diameter	161	170	164
Thick diameter	60	70	50
Lymph nodes, mm			
The largest short diameter	9	ND	2.7
PET/CT, SUV			
Spleen	ND	4.3	6.9
Lymph nodes	ND	–	14.1
Liver	ND	–	6.0
Bone	ND	3.6	5.0
Complete blood count			
WBC, $\times 10^9$/L	41.33	26.81	24.09
Hb, g/dL	9.6	14.1	12.1
PLT, $\times 10^9$/L	219	139	184
Blood biochemistry			
LDH, U/L	145	211	1473
β2-MG, mg/L	6.19	2.86	6.04
PL, %	72.3	73.2	83.8
Flow-based immunophenotype			
Abnormal cells, %	75.36	63.78	24.61
CD19, CD20, CD22, CD79b, FMC7, CD11c, CD200	+	+	+
CD10, CD103, CD123	–	–	–
CD5	–	–	+
CD23	+	+	–
Cytogenetic examination			
Karyotype	Normal	Normal	Highly complex[a]
P53 abnormalities			
Deletion 17p, %	–	73.5	20.0
TP53 mutation, %	3.24	ND	14.9
MYD88 mutation, %	29.08	–	11.20

[a], highly complex karyotype was defined as the presence of at least five chromosomal abnormalities. Patient 3 had highly complex karyotype, which was 44, X, -Y-8, +14, i (17) (q10), –20, –21, +mar (8)/46, XY[8]. M, male; NA, not available; PET/CT, positron emission tomography/computed tomography; SUV, the standardized uptake value; ND, not done; WBC, white blood cell count; Hb, Hemoglobin; PLT, blood platelet; LDH, lactic dehydrogenase; β2-MG, beta-2 microglobulin; PL, the proportion of prolymphocytes among peripheral blood lymphocytes; –, negative; +, positive.

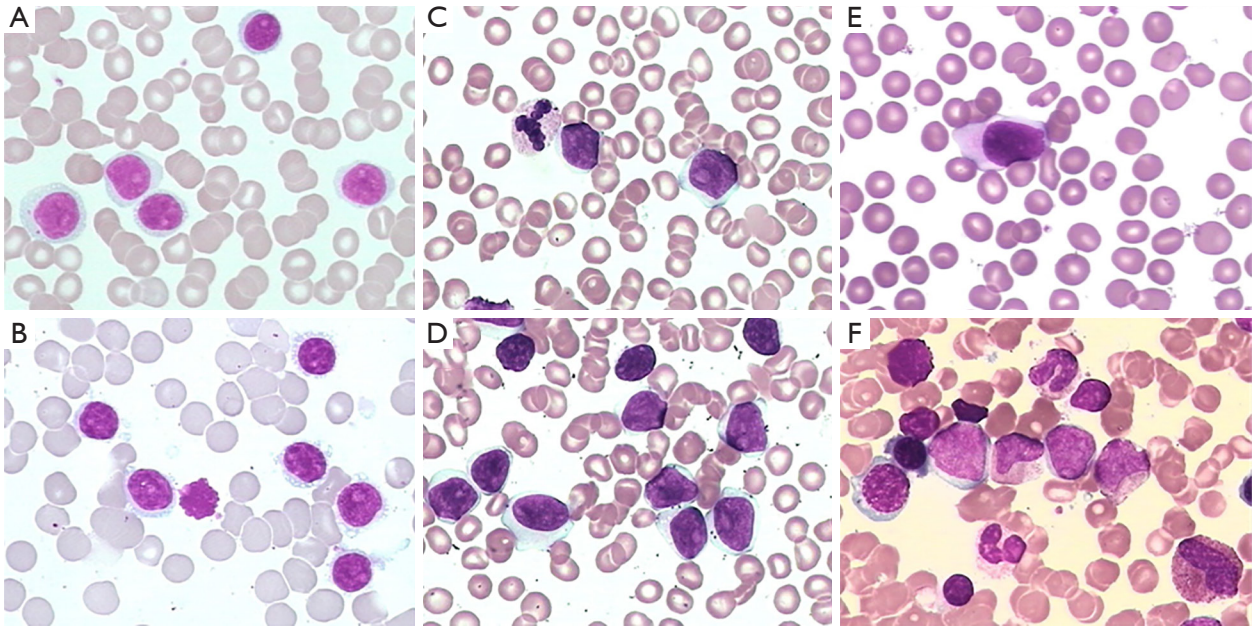

Figure 1 Prolymphocyte morphology of patients 1, 2, and 3 in the peripheral blood (A,C,E) and bone marrow (B,D,F). The common characteristics included medium to large cells with a regularly round nucleus, condensed chromatin, prominent central nucleolus, and moderately abundant cytoplasm (Giemsa staining; magnification, 10×100).

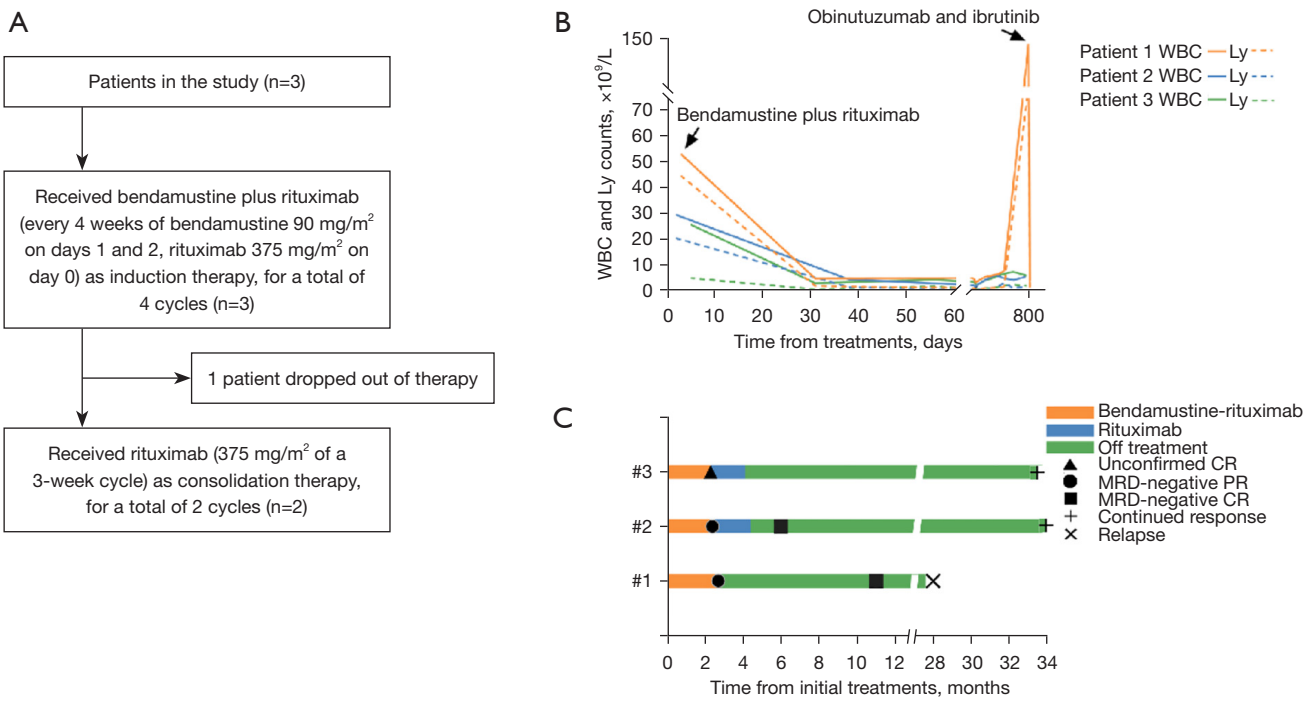

Figure 2 The treatments and survival outcomes of the three patients. Unconfirmed CR: patients without restaging bone marrow biopsies, meeting IWCLL clinical and laboratory complete remission criteria were considered to have unconfirmed complete remission. WBC, white blood cell count; Ly, lymphocyte; MRD, minimal residual disease in bone marrow; CR, complete remission; PR, partial remission; IWCLL, International Workshop on Chronic Lymphocytic Leukemia.

3 weeks for a total of two treatment cycles. Adverse events were evaluated according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. A grade 3 leukocytopenia and thrombocytopenia toxicities were observed in two patients. Patient 3 developed allergic purpura in the neck and lower limbs during the second BR treatment. Despite two of the patients being older than 65 years, the treatments were well tolerated.

After a course of BR treatment, the leukocyte and lymphocyte count rapidly decreased to normal levels (*Figure 2B*). Finally, according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, two patients remarkably attained CR with minimal residual disease (MRD) negativity in the bone marrow. Another patient attained unconfirmed CR (CRu), with a five-point Deauville score of 1 based on PET/CT and prolymphocytes disappearing in the PB smear. Two patients had an ongoing response at 33 and 34 months, respectively, while one patient suffered disease recurrence with lymphocytosis (76.05×10^9/L) and splenomegaly at 25 months after initial treatments. He was treated with obinutuzumab and ibrutinib and achieved a second remission that lasted for 12 months (*Figure 2B,2C*).

The timeline of diagnosis and treatment is depicted in *Figure 3*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In 2008, the 4th World Health Organization (WHO) classified B-PLL as an independent mature B-cell lymphoma disorder (9). To diagnose B-PLL, the fraction of prolymphocytes within the PB should be greater than 55%. Recently, due to the heterogeneity of individual patients, the 5th WHO reclassified this disease into three groups (10). In this study, cases 1 and 2 were reclassified as splenic B-cell lymphoma/leukaemia with prominent nucleoli, whereas case 3 was reclassified as prolymphocytic progression of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). B-PLL usually presents with a rapidly rising WBC count, massive splenomegaly, no or minimal lymph node enlargement, and B symptoms (i.e., fever, weight loss, night sweats) (2). To date, no immunophenotype specific to B-PLL has been identified. Cytogenetic analysis has shown the complex karyotype to be the most common, while the most common cytogenetic abnormalities detected are *MYC* translocation, deletions of 17p and 13q, and trisomy 3, 12, and 18. *MYC* translocation or gain is associated with the pathogenesis and adverse clinical outcomes of B-PLL (11). In addition, P53 abnormalities are routinely observed in 75% of B-PLL patients (12), which is significantly higher than that in other B-cell lymphomas and may participate in the pathogenesis of B-PLL. A previous study confirmed that the median OS of B-PLL patients with 17p deletion and *MYC* aberration was less than 1 year (11). All three patients in the present study presented P53 abnormalities. *BCOR* mutation, which is only found in splenic diffuse red pulp small B-cell lymphoma (SDRPL), was detected in one patient. It has been reported that B-PLL might be characterized by the presence of *BCOR* mutation and *MYC* translocation (11).

Due to the scarcity of B-PLL, standardized treatment modalities have not been well-established. Patients with B-PLL have a worse overall prognosis than those with other B-cell lymphomas, and therefore, it is a disease of significant concern. The median OS of B-PLL before rituximab era was only 3–5 years (4,5). As shown in *Table 2*, for chemotherapy-treated cases, the therapeutic effective rate was low and exhibited difficulty in achieving CR (4,13). Rituximab monotherapy or Rituximab-based combination chemoimmunotherapy improved the survival of patients with B-PLL (6,14-16). Bendamustine, a bifunctional alkylator, offers an attractive chemotherapy option for follicular lymphoma (FL), mantle cell lymphoma (MCL), and CLL. Some studies have demonstrated that the BR regimen has a non-inferior PFS over rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the first-line treatment of indolent NHL or MCL. And BR has a lower toxicity profile than R-CHOP (7,8,17).

In this series, three patients with high tumour burden achieved good clinical outcomes and tolerated the BR regimen well. The results were consistent with STIL NHL1-2003 and BRIGHT inferiority trials (8,17). Meanwhile, the anti-CD20 antibody, rituximab, as a maintenance therapy, plays an important role in mature B-cell lymphomas, especially in FL and MCL (18,19). Rituximab consolidation improved the PFS in two patients,

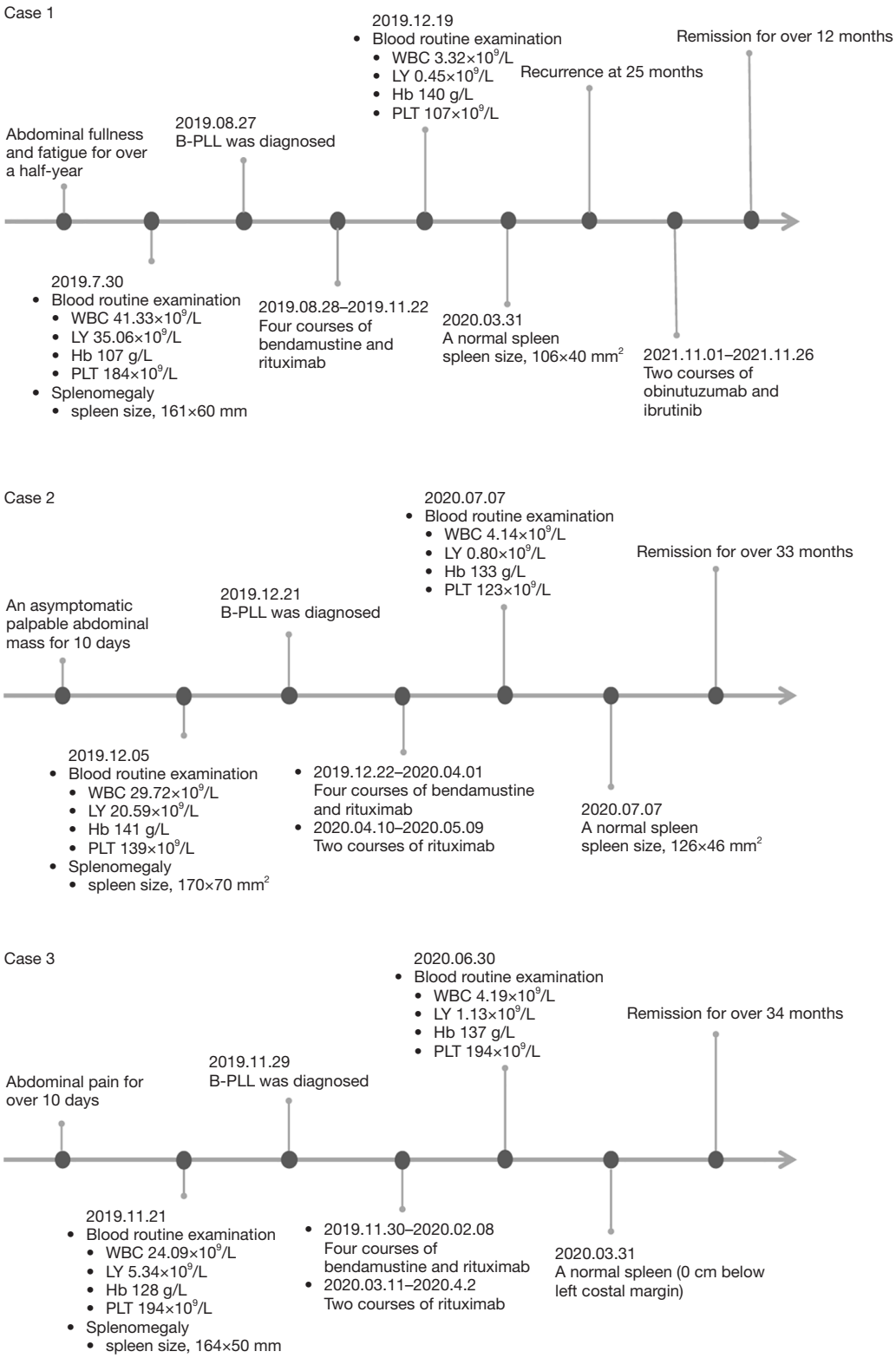

Figure 3 Timeline for diagnosis and treatment in three cases. WBC, white blood cell count; LY, lymphocyte count; Hb, Hemoglobin; PLT, platelet count; B-PLL, B-cell prolymphocytic leukemia.

Table 2 Characteristics and survival of patients with B-PLL after treatment with different strategies

Reference	N	Line	Regimens	Age (years), median [range]	Genetic abnormalities	Outcome
Shvidel *et al.*	35	1	CP/COP (n=17) CHOP (n=6) 2CdA (n=6) Untreated (n=6)	68 [43–86]	NA	CR (1/29), PR (13/29) Median follow-up time: 63 months Median OS: 65 months
Hercher *et al.*	41	1	Splenic irradiation/ splenectomy/single- or multiple-drug chemotherapy regimens (CHOP, COP, fludarabine, and chlorambucil with or without corticosteroids) (n=30)	67 [42–89]	*TP53* mutations (6/16)	CR (1/30), PR (8/30) Median PFS: 37 months
			Untreated (n=11)			Median OS: 60 months
Mourad *et al.*	1	1	Rituximab	64	NA	Keep CR for 8 months
Chow *et al.*	4	1	FER (n=4)	69.5 [55–84]	17p deletion (1/4) 13q deletion (2/4) 14q deletion (1/4)	CR (4/4) PFS: +26–+83 months OS: 26–+84 months
Oka *et al.*	1	1	Ibrutinib	71	17p deletion	Keep CR for 12 months
Moore *et al.*	6	1	Ibrutinib, rituximab and alemtuzumab (n=2), ibrutinib and rituximab (n=2), ibrutinib (n=2)	67.3 [62.9–≥90]	17p deletion (5/6) *TP53* mutations (4/6)	CCR (3/6), PR (2/6), SD (1/6) Follow-up time: 2.5–50.5 months Median PFS: 34.7 months (range, 2.6 to +50.5 months) Median OS not reached
Eyre *et al.*	8	1 (n=4) >1 (n=4)	Idelalisib-rituximab	64.5 [57–76]	17p deletion (7/8) *TP53* mutations (3/8)	CR (7/8), PR (1/8) Median follow-up time: 21 months Median CR duration (5/8): 26 months
Xing *et al.*	1	1	Zanubrutinib, rituximab and lenalidomide	52	*MYC* and *TP53* mutations	Keep MRD negative CR for 12 months
Chen *et al.*	1	2	Venetoclax	63	*TP53* mutation and 17p deletion	Keep MRD negative CR for nearly 4 years

B-PLL, B-cell prolymphocytic leukemia; CP, chlorambucil + prednisone; COP, cyclophosphamide + vincristine + prednisone; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; 2CdA, 2-chlorodeoxyadenosine; CR, complete remission; PR, partial remission; OS, overall survival; PFS, progression-free survival; FER, fludarabine + epirubicin + rituximab; CCR, clinical complete remission; SD, stable disease; +, ongoing; MRD, minimal residual disease.

indicating that rituximab maintenance for B-PLL is worthy of further exploration. Additionally, at present the development of B-cell malignancies is dependent on the activation of B-cell receptor (BCR) signaling. BCR inhibitors (ibrutinib and idelalisib) have shown significant efficacy in treating patients with B-PLL, especially patients with a high-risk cytogenetic abnormality (20,21,22). A recently published study revealed that MRD-negative CR was sustained for 12 months in a high-risk (*TP53* and *MYC* abnormalities) patient treated with zanubrutinib, rituximab, and lenalidomide (ZR2) (23) (*Table 2*). The treatment of such patients is undergoing a paradigm shift

to chemo-free, which might be considered a novel option for elderly patients who cannot tolerate chemotherapy. One patient in our series who had disease progression responded to ibrutinib-based combination therapies. It is suggested that the individualization of therapy, including the combination of ibrutinib or bendamustine with an anti-CD20 monoclonal antibody, should be considered based on the clinical evidence (high-risk patients as well as those with a high tumor burden or high-risk cytogenetics). Meanwhile, the sequential consolidation and maintenance therapies of ibrutinib or an anti-CD20 monoclonal antibody monotherapy or combination therapy may further deepen remission and improve survival. Also, venetoclax monotherapy has been demonstrated to be efficacious in patients with relapsed/refractory B-PLL (24). Further treatment with allogeneic hematopoietic stem cell transplantation (Allo-HSCT) could also be considered as a first-line treatment in young responders and is the only current treatment that is likely capable of curing B-PLL patients (25).

The short-term results of our case series using BR as the first-line treatment of B-PLL with high tumour burden are promising. Therefore, it deserves further study and clinical application. At present, more and more patients with p53 abnormalities receive a Bruton tyrosine kinase (BTK) based first line treatment. Further investigation of the optimal treatment strategy in the era of targeted therapy is needed.

Conclusions

Overall, the results of this study support the idea that the BR regimen and rituximab consolidation are potent agents to obtain deep and durable remission in B-PLL. However, our study has some limitations, namely its small sample size and insufficient follow-up time. Therefore, there is a pressing need for prospective clinical trials to confirm the efficacy of the BR regimen in B-PLL.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-828/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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