

Chinese expert consensus on oral drugs for the treatment of mature B-cell lymphomas (2020 edition)

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Abstract Oral drugs such as ibrutinib play an important role in the treatment of mature B-cell lymphoma (BCL) due to their reliable efficacy, manageable safety, high accessibility, and convenience for use. Still, no guidelines or consensus focusing on oral drug therapies for BCL is available. To provide a reference of oral agent-based treatment for mature BCL, a panel of experts from the Lymphocyte Disease Group, Chinese Society of Hematology, Chinese Medical Association conducted an extensive discussion and reached a consensus on oral drugs for Chinese BCL patients on the basis of the current application status of oral drugs in China, combined with the latest authoritative guidelines in the world and current research reports. This consensus reviewed the application of oral drugs in the treatment of BCL and the latest research and provided appropriate recommendations on the use of oral drugs for indolent or aggressive BCL patients. With the deepening of research and the development of standardized clinical applications, oral medications will bring better treatment to BCL patients, enabling more patients to benefit from them.

Keywords B-cell lymphoma; oral drug; targeted therapy; immunotherapy; COVID-19 pandemic

Introduction

Mature B-cell lymphoma (BCL) is a common hematological malignancy, and patients often need long-term regular treatment. BCL has various pathological types, and their treatment principles are different. In recent years, with continuous breakthroughs in the research and development of oral drugs, oral targeted drugs used for BCL treatment either as monotherapy or in combination with chemotherapy have been confirmed to achieve better curative effects or delay recurrence for some patients with indolent or aggressive lymphoma. In the context of the current global spread of coronavirus disease 2019 (COVID-19), it is particularly important for BCL patients with low immunity to choose appropriate treatment and

minimize hospital visits. A well-controlled disease by oral drugs can reduce the frequency of admission and cut off the transmission route, thereby reducing the risk of SARS-CoV-2 infection [1] and improving quality of life. Novel oral drugs have the advantages of high accessibility, convenient use, reliable efficacy, and manageable safety. Still, no established standard about the application of oral drugs for BCL is available. To further provide patients with safe and effective treatment, a number of experts conducted an extensive discussion and developed this consensus based on the current Chinese and authoritative international guidelines for oral treatment of BCL. This consensus will be updated regularly with the progress of Chinese and international clinical research on BCL treatment.

Methodology

This consensus was initiated by the Lymphocyte Disease Group, Chinese Society of Hematology, Chinese Medical Association and jointly formulated by the Chinese

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The official websites of the CSCO, National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and American Society of Hematology and databases including PubMed and CNKI were used to search the scientific literature involving treatments comprising oral drugs for BCL patients. A broad search was conducted for literature published before December 30, 2020, including practical guidelines, consensus, clinical trials, systematic reviews, meta-analyses, conference presentations, real-world studies, and reviews. On screening for relevance, 62 articles were included in this consensus. The guidelines and consensus that are referred to in this article mainly included the 2020 CSCO guideline [2], the 2020 NCCN guidelines [3–5], the 2017 ESMO guideline [6], and the 2020 consensus of the Asian Lymphoma Study Group [7].

The recommendations in this consensus were developed using the modified Delphi formal consensus methodology [8,9]. First, a subgroup of the expert panel drafted the recommendations on the basis of available evidence and clinical expertise, and these recommendations were reviewed and refined by the principal expert members ($n = 4$) meeting in person. Additional experts ($n = 30$) were then recruited as the supplemented expert panel to rate their agreement with the recommendations using a 5-point scale from “strongly agree” to “strongly disagree.” The entire membership of 34 experts is referred to as the consensus panel. A consensus was defined as agreement by $\geq 75\%$ of raters. A “strong” recommendation level was assigned when the voting rate of agreement was $\geq 90\%$; otherwise ($\geq 75\%$ and $< 90\%$), a “moderate” rating was assigned. The final version of this consensus document was developed on the basis of input and comments from all members of the expert panel.

Overview of mature BCL

According to pathological changes, lymphoma can be divided into two categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Almost all HL cells are derived from B cells, and only a few are derived from T cells. According to the 2016 WHO Classification of Lymphohematopoietic Neoplasms [10], HL can be subdivided into classical HL and nodular lymphocyte-predominant Hodgkin lymphoma. In NHL, about 85%–90% are of B-cell origin [11]. The occurrence and development of BCL involve a variety of molecular pathways, such as B-cell receptor (BCR) signaling pathway, B-cell lymphoma/leukemia 2, Toll-like receptor signaling pathway, programmed cell death protein 1/programmed cell death protein ligand 1 signaling

pathway, and nuclear transcription factor κ B.

Oral drugs for BCL

Oral drugs are increasingly being used in the treatment of BCL. At present, many drugs are already in the application or marketing stage. This consensus only introduces the oral drugs marketed in China.

Targeted drugs

Among the novel biological therapies in BCL, the development of small-molecule inhibitors (SMIs) with different mechanisms of action is encouraging and exciting. Thus far, the only oral SMIs approved in China are BCR signaling blockers.

Bruton's tyrosine kinase inhibitors (BTKi)

The continuous abnormal activation of the BCR signaling pathway is highly related to the survival of patients and the malignant proliferation of tumors. Bruton's tyrosine kinase (BTK) is a non-receptor kinase that plays an important role in promoting cancer signal transduction. BTK is essential for the survival of a variety of B-cell malignant cells [12] and is also a crucial target for the treatment of BCL. BTKi is a targeted inhibitor designed for BTK by blocking the conduction of the BCR signaling pathway; it has become an important direction for the treatment of B cell-related diseases [13]. Currently, two BTKis are approved in China: ibrutinib and zanubrutinib.

Ibrutinib

As the first-in-class oral BTKi (once daily), ibrutinib has been approved in the United States (US) and China for the treatment of various BCLs. Ibrutinib is a small-molecule kinase inhibitor that selectively and irreversibly inhibits BTK and interleukin-2-inducible T cell kinase through covalent bonding. Ibrutinib has been approved by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory (R/R) mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), R/R marginal zone lymphoma (MZL), and R/R chronic graft-versus-host disease. Ibrutinib was approved in China in 2017 and was added to the Chinese National Reimbursement Drug List (NRDL) in 2018. In China, ibrutinib monotherapy was approved to treat patients with MCL who have received at least one prior therapy, patients with WM who have received at least one prior therapy or who are treatment-naïve (TN) and not suitable for chemoimmunotherapy, and patients with CLL/SLL. Combined with rituximab, ibrutinib is suitable for patients with WM. A number of

real-world studies on ibrutinib have shown that it can significantly improve progression-free survival (PFS) and overall survival (OS) of patients with MCL, WM, or CLL [14–17]. Ibrutinib has high accessibility and wide application and currently has abundant long-term clinical follow-up data.

Zanubrutinib

Zanubrutinib is a selective and irreversible BTKi with good oral bioavailability. Zanubrutinib was approved in the US in 2019 and China in 2020 for adult MCL patients who have received at least one prior therapy and adult CLL/SLL patients who have received at least one prior therapy. However, it has not been added to the Chinese NRDL. Due to the short marketing time of zanubrutinib, clinical follow-up data and real-world study involving zanubrutinib are limited.

Immunomodulator

Lenalidomide

Lenalidomide is an oral immunomodulatory drug that has anti-angiogenesis and anti-tumor activities. The indirect mediation of lenalidomide is exerted by a variety of immune cells found in the tumor microenvironment, such as B cells, T cells, natural killer cells, and dendritic cells. E3 ubiquitin ligase may be the primary target of lenalidomide in tumor cells and tumor niches [18]. Lenalidomide is approved in the US for the treatment of myelodysplastic syndrome, multiple myeloma, R/R MCL, R/R MZL, and R/R follicular lymphoma (FL). However, the indication approved and included in the NRDL in China is only combined with dexamethasone for the treatment of adult patients with multiple myeloma who have not been treated before and are not suitable for transplantation or adult patients with multiple myeloma who have received at least one prior therapy. In the treatment of BCL, lenalidomide is mostly used in combination with other drugs, as its efficacy as monotherapy is unsatisfactory.

Other drugs

Chlorambucil

Chlorambucil is a traditional nitrogen mustard anti-tumor chemotherapy drug. It is widely used to treat lymphoma, leukemia, and other diseases. Chlorambucil leads to DNA interstrand cross-links, inhibits DNA replication, and exerts an inhibitory effect on tumors. Chlorambucil has been added to the NRDL in China. Its indications include HL, several NHLs, CLL, WM, and advanced ovarian adenocarcinoma. Because of its low cost and convenient

oral application, chlorambucil was used as a first-line treatment for some lymphomas. It has been widely used and has achieved certain effects [19], but its response rate is low when used as a single agent. Chlorambucil is being replaced by targeted drugs.

Cyclophosphamide

Cyclophosphamide is currently a widely used anticancer drug that transfers alkyl groups to the DNA of cancer cells to cause DNA breakage, thus inhibiting DNA synthesis and inducing cell apoptosis. In 1954, cyclophosphamide was first approved by the FDA as a standard anticancer drug. Currently, it is mostly used in the treatment of malignant lymphoma, acute lymphocytic leukemia or CLL, and multiple myeloma.

Glucocorticoids

Glucocorticoids inhibit lymphocytes and are used in the treatment of hematological malignancies such as acute lymphoblastic leukemia, lymphoma, and multiple myeloma. However, glucocorticoid monotherapy has limited efficacy for lymphoma, and it is generally used as a component of combination therapy. Long-term application of glucocorticoids can cause a series of adverse effects, and the severity of these adverse effects is proportional to the dosage of glucocorticoids and duration of treatment.

Oral drug treatment recommendations for mature BCL

Treatment of indolent BCL

Indolent B-cell non-Hodgkin lymphoma is a type of NHL that includes several subtypes, which have pathological characteristics such as low malignancy, slow progression, and slow transformation of tissue types to aggressive lymphomas. Its subtypes include CLL/SLL, WM/LPL, MZL, FL, and a fraction of MCL.

CLL/SLL

Expert recommendation 1

◆ For TN CLL/SLL patients with or without del(17p)/*TP53* mutation, the recommended preferred oral drug is ibrutinib monotherapy; zanubrutinib monotherapy can also be considered.

◆ Recommendation level: strong (voting rate of agreement: 90%).

◆ For patients with R/R CLL/SLL, the recommended preferred regimen is ibrutinib monotherapy; other regimens, including zanubrutinib monotherapy or lenalidomide with or without rituximab, can also be considered.

◆ Recommendation level: strong (voting rate of agreement: 90%).

In the second edition of the 2021 NCCN guidelines [20], oral drugs occupy an important position in the initial treatment of CLL/SLL. Notably, ibrutinib is the only single agent recommended for all types of CLL/SLL and is one of the preferred regimens and a category 1 recommendation for first-line or R/R therapy of CLL/SLL. In the 2020 Chinese guidelines [2], ibrutinib was recommended for the treatment of naïve patients with CLL/SLL as a category 1 recommendation regardless of whether there are del(17p)/*TP53* gene mutations and severe frailty. For R/R patients, oral ibrutinib is also a category 1 recommendation. The category 2 recommendation involves zanubrutinib monotherapy and lenalidomide with or without rituximab.

A number of clinical trials (NCT01520519, NCT01578707, and NCT01722487) showed that ibrutinib was well tolerated and could improve PFS, OS, and overall response rate (ORR) either in monotherapy or combination therapy for CLL/SLL [21–24]. A phase III study (RESONATE study, NCT01578707) [25] compared the efficacy and safety of ibrutinib versus ofatumumab and showed that ibrutinib monotherapy is more effective than ofatumumab in the treatment of patients with R/R CLL/SLL (including patients with high-risk clinical or genomic characteristics); the median PFS of the ibrutinib group was significantly prolonged compared with that of the ofatumumab group (44.1 vs. 8.1 months), and the median OS was 67.7 months in the ibrutinib group and 65.1 months in the ofatumumab group during the 6-year follow-up. In the RESONATE-2 trial (NCT01722487 and NCT01724346) comparing the efficacy and safety of ibrutinib versus chlorambucil in TN CLL/SLL [26], ibrutinib fared better than chlorambucil in terms of 5-year PFS (70% vs. 12%) and OS (83% vs. 68%), with an ORR of 92% for ibrutinib. According to a long-term follow-up study (8 years) on the treatment of first-line and R/R CLL/SLL with ibrutinib (NCT01105247, NCT01109069) [27], the responses of CLL/SLL patients on ibrutinib monotherapy were sustained, the long-term survival benefits were confirmed, and long-term tolerability was observed.

In a phase 2 registration study (NCT03206918) in China, the treatment of R/R CLL/SLL patients with zanubrutinib was well tolerated and resulted in a high ORR of 84.6% [28]. The 12-month event-free rate for the duration of response (DOR) was 92.9%. The 12-month OS rate was 96%. Eight (9.0%) patients discontinued zanubrutinib due to toxicities, and seven (8.0%) patients required at least one dose reduction.

The MD Anderson Cancer Center of the University of Texas conducted a study on the efficacy of lenalidomide combined with rituximab in the treatment of CLL (NCT01446133) [29]. Among the 55 TN patients and 53

relapsed patients who were evaluable, 12 patients discontinued treatment before the first response assessment (8 patients with toxicities, 3 patients lost to follow-up, and 1 patient died). The median follow-up time was 33 months for TN patients and 25 months for R/R patients. The ORR was 73% for TN patients and 64% for R/R patients. The CR was 35% for TN patients and 28% for R/R patients.

WM

Expert recommendation 2

- ◆ For TN WM patients, oral ibrutinib with or without rituximab is recommended, especially for those who are not suitable for chemotherapy and immunotherapy.
- ◆ Recommendation level: strong (voting rate of agreement: 100%).
- ◆ For patients with R/R WM, giving priority to ibrutinib with or without rituximab is recommended for the first relapse if not previously given.
- ◆ Recommendation level: strong (voting rate of agreement: 90%).

WM is a rare type of indolent mature BCL, which accounts for < 2% in NHL [30]. In the first edition of the 2021 NCCN guidelines [5], ibrutinib is the only oral therapy that is included in the preferred regimens. For TN and relapsed WM patients, ibrutinib with or without rituximab is listed as the preferred recommended regimen (category 1 recommendation). The 2016 edition of the Chinese expert consensus on diagnosis and treatment for LPL/WM [30] also recommended ibrutinib for TN and R/R WM patients.

A critical phase II clinical trial (NCT01614821) in the US [31] showed that the ORR of WM patients treated with ibrutinib was 90.5% and that the main remission rate was 73.0%. MYD88^{L265P}CXCR4^{WT} patients achieved the highest efficacy, with an ORR of 100% and main remission rate of 91.2%. The estimated 2-year PFS and OS of all patients were 69.1% and 95.2%, and the estimated 5-year PFS and OS of all patients were 54% and 87%, respectively. A phase III trial (NCT02165397) showed that the total effective rate of ibrutinib monotherapy in patients with rituximab-refractory WM was 90%, 71% of patients achieved major remission, and the 18-month PFS rate was 86% [32].

According to the results of the ASPEN Phase III clinical trial (NCT03053440) of zanubrutinib versus ibrutinib for the treatment of WM patients [33], the zanubrutinib group had a higher very good partial remission rate than the ibrutinib group but failed to achieve a statistically significant difference (28.4% vs. 19.2%, $P = 0.0921$) due to the short follow-up time. At 18 months, the progression-free rate and estimated OS rate were 85% and 97% in zanubrutinib group and 84% and 93% in the ibrutinib group, respectively [34].

MZL

<p>Expert recommendation 3</p> <ul style="list-style-type: none"> ◆ For patients with MZL, the recommended regimen including oral drugs for first-line therapy is lenalidomide combined with rituximab. ◆ Recommendation level: moderate (voting rate of agreement: 88.7%). ◆ For MZL patients who have failed previous therapies, the recommended preferred regimens involving oral drugs are ibrutinib monotherapy or lenalidomide combined with rituximab; another recommended regimen involving oral drugs is lenalidomide combined withobinutuzumab. ◆ Recommendation level: strong (voting rate of agreement: 93.3%).
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In the second edition of the NCCN guidelines in 2020 [3], the oral immunomodulatory regimen of lenalidomide combined with rituximab is listed as one of the first-line treatments (category 2B recommendation). Ibrutinib is listed as the second-line treatment and the only recommended single-agent oral BTKi (category 2B recommendation).

A phase II clinical study of ibrutinib combined with lenalidomide and rituximab in TN MZL patients showed that the estimated 2-year PFS was 76%, the ORR was 80%, and the CR was 60% [35].

A trial of rituximab combined with lenalidomide in the treatment of patients with MZL showed that in the absence of unexpected toxicity, the ORR was 61%, but the CR rate of 33% was similar to that of other regimens (NCT01611259) [36]. A prospective phase II trial (NCT01980628) of ibrutinib monotherapy for MZL patients who failed previous rituximab-containing regimens showed that patients achieved a certain salvage treatment effect (ORR was 48%, median PFS was 14.2 months) [37]. The median PFS of extranodal MZL, spleen MZL, and lymph node MZL was 13.8, 19.4, and 8.3 months, respectively.

FL

<p>Expert recommendation 4</p> <ul style="list-style-type: none"> ◆ For patients with FL who are not eligible for transplantation, lenalidomide combined with rituximab can be considered for first-line therapy. ◆ Recommendation level: moderate (voting rate of agreement: 83.3%). ◆ For second-line and subsequent therapy of FL patients who are not eligible for transplant, the preferred regimen involvingoral drugs is lenalidomide combined with rituximab; other recommended regimens involving oral drugs are lenalidomide monotherapy or lenalidomide combined with obinutuzumab. ◆ Recommendation level: strong (voting rate of agreement: 93.3%).

In the second edition of the NCCN guidelines in 2020 [3], the oral immunomodulatory regimen of lenalidomide combined with rituximab was listed as one of the first-line, second-line, and subsequent treatments. In addition, lenalidomide combined with obinutuzumab was also included in the first-line treatment (category 2B

recommendation). In the 2020 China guidelines [2], lenalidomide combined with rituximab was recommended as the second-line therapy.

In a phase II clinical trial (NCT01145495) of lenalidomide combined with rituximab in the treatment of FL [38], the CR rate and PFS were similar to those of chemotherapy-based treatments, but the toxicity was much lower. Moreover, the combination is a reasonable alternative immunochemotherapy. In the study of rituximab combined with lenalidomide in the treatment of advanced untreated FL (NCT01476787 and NCT01650701) [39], a total of 1030 patients were randomly assigned to receive rituximab plus lenalidomide (513 cases) or rituximab plus chemotherapy (517 cases). The CR rates of the two groups were 48% and 53%, respectively.

In addition, a phase II clinical trial of ibrutinib combined with lenalidomide in the treatment of FL showed that the 2-year PFS rate was 76%, the ORR was 97%, and the CR rate was 78% [35].

Treatment of aggressive BCL

Aggressive BCL includes MCL, diffuse large BCL (DLBCL), primary central nervous system lymphoma (PCNSL), and Burkitt's lymphoma (BL). Among them, MCL, DLBCL, and PCNSL can be treated with oral drugs.

MCL

<p>Expert recommendation 5</p> <p>A consensus could not be reached regarding the use of lenalidomide combined with rituximab as one of the induction regimens for TN MCL patients.</p> <ul style="list-style-type: none"> ◆ For relapsed and refractory MCL patients, the preferred regimens involving oral drugs are ibrutinib with or without rituximab, lenalidomide with or without rituximab, or zanubrutinib monotherapy; another recommended regimen involving oral drugs is rituximab combined with ibrutinib and lenalidomide. ◆ Recommendation level: strong (voting rate of agreement: 93.3%).
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For TN patients, lenalidomide combined with rituximab is listed as one of the first-line less aggressive therapy in the second edition of the NCCN guidelines in 2020 [3].

Traditional salvage chemotherapy has limited efficacy in patients with R/R MCL. The 2017 ESMO guidelines pointed out that new targeted drugs should be considered a priority for early relapsed cases [6]. Among the approved drugs, ibrutinib has the highest remission rate and, in some cases, even obtains long-term remission. In the second edition of the NCCN guidelines in 2020 [3], second-line patients whose first-line treatment only achieves PR by chemoimmunotherapy were recommended to receive ibrutinib with or without rituximab, zanubrutinib, or acalabrutinib. For those with a

long duration of remission (> expected median PFS), SMIs such as ibrutinib are also recommended. The 2020 China guidelines pointed out that the most effective BTKis, such as ibrutinib, zanubrutinib, or a combination of these drugs with rituximab and lenalidomide, are currently considered to be the most effective therapy [2].

A phase II trial (NCT01472562) of lenalidomide combined with rituximab in TN MCL patients showed that the ORR was 92%, the CR was 64%, the median PFS was not reached within a median follow-up of 30 months, the 2-year PFS rate was 85%, and the 2-year OS rate was 97% [40].

The phase II PCYC-1104 trial (NCT01236391) of ibrutinib monotherapy for R/R MCL showed that the ORR was 68%, the CR rate was 21%, and the median DOR was 17.5 months [41]. The phase III clinical trial (NCT01646021) of ibrutinib versus sirolimus showed that in the treatment of previously treated patients with R/R MCL, the ORRs of the ibrutinib and sirolimus groups were 77% and 46%, and the 2-year PFS rates were 41% and 7%, respectively [24]. A pooled analysis in R/R MCL patients enrolled in the PCYC-1104 (NCT01236391), SPARK (NCT01599949), and RAY (NCT01646021) trials showed that second-line ibrutinib, after a median follow-up of 3.5 years, had a median PFS of 25.4 months, an ORR of 77.8%, and a DOR of 35.6 months; however, a median OS was not reached [42]. For third and subsequent lines, the median PFS was 10.3 months, the median OS was 22.5 months, the ORR was 66.8%, and DOR was 16.6 months [42].

A study of zanubrutinib for MCL patients showed promising efficacy, with a CR rate of 68.6%, but the median PFS was only 22.1 months [43]. Whether the remission rate can be converted into a survival benefit remains to be confirmed; moreover, the response rate of patients > 65 years was poor, and the reason was not clear (NCT03206970) [43].

DLBCL

Expert recommendation 6

- ◆ For TN non-germinal center (non-GCB) DLBCL patients (< 60 years), ibrutinib combined with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) might significantly improve the survival outcome, and the safety is controllable.
- ◆ Recommendation level: moderate (voting rate of agreement: 83.3%).
- ◆ For R/R non-GCB DLBCL patients who are not eligible for transplant, ibrutinib monotherapy or lenalidomide combined with rituximab can be considered.
- ◆ Recommendation level: moderate (voting rate of agreement: 76.7%).

In the second edition of the NCCN guidelines in 2020 [3], ibrutinib monotherapy and lenalidomide combined with rituximab are listed as the second-line treatment of non-GCB DLBCL patients. The 2020 Chinese guidelines [2]

listed ibrutinib as the only oral BTKi monotherapy for R/R DLBCL, and lenalidomide combined with rituximab can also be recommended for R/R DLBCL.

The global multicenter phase III PHOENIX trial (NCT01855750) evaluated the efficacy of ibrutinib combined with R-CHOP versus placebo plus R-CHOP in the first-line treatment of non-GCB DLBCL patients. The results showed that ibrutinib combined with R-CHOP improved event-free survival (HR 0.579), PFS (HR 0.556), and OS (HR 0.330) in patients younger than 60 years [44]. The exploratory analysis data from the Chinese cohort also showed that patients younger than 60 years treated with ibrutinib plus R-CHOP had better PFS (HR 0.480) and OS (HR 0.426) [45].

In a phase I/II clinical trial involving 80 patients with R/R DLBCL, 37% of non-GCB DLBCL patients achieved CR or PR under ibrutinib treatment (NCT00849654 and NCT01325701) [46]. A phase II clinical trial (NCT00294632) of lenalidomide combined with rituximab in the treatment of R/R DLBCL, FL, and transforming lymphoma [47] showed that the ORR was 33%, the median DOR was 10.2 months, and the median PFS and OS were 3.7 and 10.7 months, respectively.

A more recent phase II trial (NCT02753647) treated 49 elderly patients newly diagnosed with DLBCL (international prognostic index ≥ 2) with the combination of histone deacetylase inhibitor (HDACI) tucidinostat and R-CHOP; the results showed that this combination was well tolerated, the response rate was high (ORR of 94%, CR rate of 86%), and the PFS and OS rates were 68% and 80%, respectively, at 2 years [48].

PCNSL

Expert recommendation 7

- ◆ For patients with primary PCNSL or R/R PCNSL who have not been treated with ibrutinib, ibrutinib monotherapy or ibrutinib combined with chemotherapy can be considered.
- ◆ Recommendation level: strong (voting rate of agreement: 96.7%).

PCNSL is a rare type of aggressive extranodal NHL, and 90%–95% of PCNSL are of the diffuse large B-cell type and originate in the brain, spinal cord, eyes, or pia mater, without systemic involvement. Lionakis *et al.* [49] (NCT02203526) found that the mutation rates of CD79B and MYD88^{L265P} in PCNSL were high. CHOP-like chemotherapy was usually used to treat PCNSL, but the effect was limited. Even though rituximab was added to chemotherapy, the improvement of the efficacy was still unsatisfactory. This is caused by the low blood–brain barrier permeability of rituximab and other drugs. Ibrutinib has been demonstrated to have excellent activity in tumors with CD79B and MYD88^{L265P} mutations [46]. At the same time, as a small molecule, ibrutinib can pass

through the blood–brain barrier to reach central lesions. Preclinical mouse experiments have shown that ibrutinib can quickly cross the blood–brain barrier within 0.29 h, with a maximum concentration ratio of 0.7 in the brain and plasma, and ibrutinib can effectively inhibit the BCR signaling pathway in central lesions [50]. The application of ibrutinib will improve the outcome and prognosis of PCNSL.

Grommes *et al.* [51] (NCT02315326) conducted a dose-escalation study of ibrutinib in patients with primary or advanced central nervous system lymphoma, and the dose was gradually increased from 560 mg/day to 840 mg/day until progressive disease. The results showed that in 13 PCNSL patients, 10 patients had a clinical response (5 patients achieved CR, and 5 patients achieved PR), the ORR was 77%, the median PFS was 4.6 months, and the median OS was 15 months. Lionakis *et al.* [49] (NCT02203526) conducted a proof-of-concept study of ibrutinib monotherapy and ibrutinib combined chemotherapy (DA-TEDDi-R). Among 18 patients with PCNSL, 94% of patients had tumor reduction after ibrutinib monotherapy, including PCNSL patients with CD79B and/or MYD88 mutations, and 86% of evaluable patients reached CR after DA-TEDDi-R treatment.

Summary of oral medication for mature BCL

According to the different pathological types of BCL, the experts summarized the treatment procedures involving oral agents in Fig. 1 and the medicine instruction in Table 1.

Management of mature BCL in the COVID-19 pandemic

During the COVID-19 pandemic, patients with malignant hematological tumors are potentially at high risk of infection due to their own weakened state, immunosuppressive treatment, frequent hospital visits, and the elderly age of some patients with multiple comorbidities. Once infected, it is difficult to produce effective specific antibodies to eliminate SARS-CoV-2 for these patients, and the disease can progress rapidly. Studies have shown that the death rate of COVID-19 patients with hematological malignancies was higher than that of patients with solid tumors [52]. A study on COVID-19 patients with malignant hematological tumors in Italy (NCT04352556) [53] showed that the mortality rate of such patients was 37%, and the prognosis of COVID-19 patients with malignant hematological tumors was poorer than those without infection. Therefore, active infection prevention strategies need to be adopted before effective vaccines or treatment strategies are available. For patients with BCL, the intensity of treatment can be minimized under the premise of disease control. In areas with severe epidemics, hospitals are high-risk areas, and patients in stable conditions who do not rely on blood transfusions should try their best to be observed at home and maintain oral medication. Monoclonal antibodies and small-molecule targeted therapy should be used as much as possible for treatment. Patients with stable disease can be treated with BTKis, immunomodulators, and other

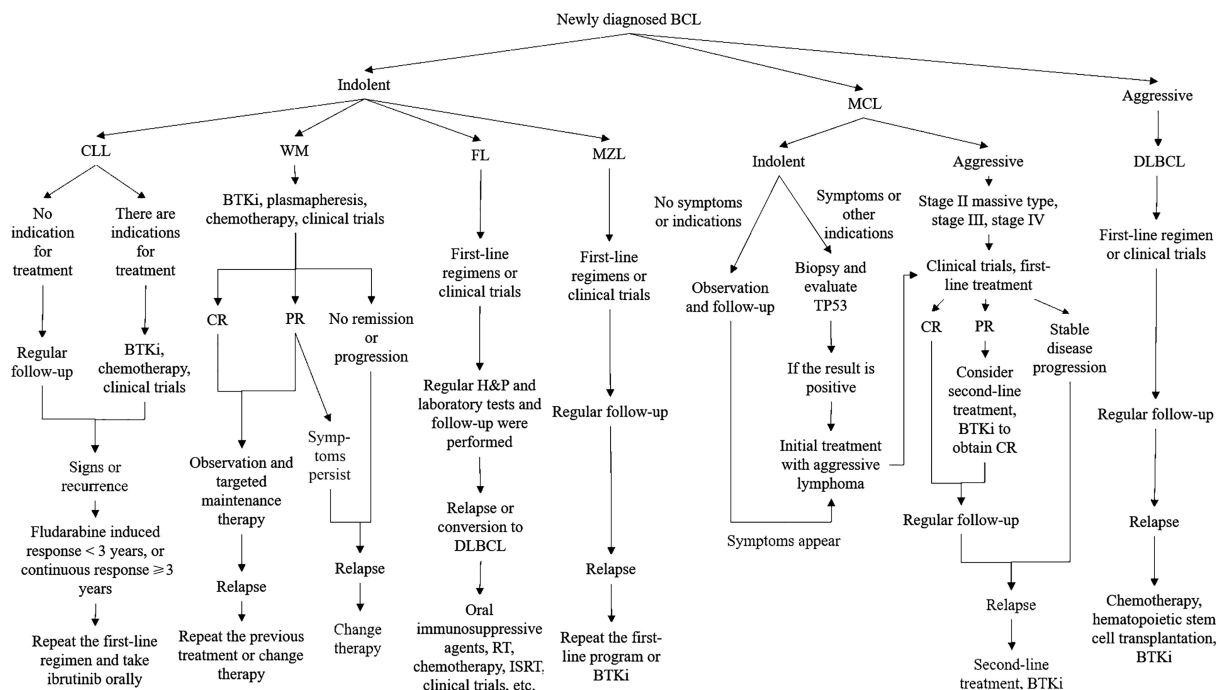


Fig. 1 Flowchart of oral drug treatment for mature B-cell lymphoma (BCL).

Table 1 Summary of oral drugs for BCL^a

Classification	Disease	Application of oral drugs	
Indolent BCL	CLL/SLL	TN: 1. Ibrutinib (420 mg, orally, once daily) 2. Zanubrutinib (160 mg, orally, twice daily)	R/R: 1. Ibrutinib (420 mg, orally, once daily) 2. Zanubrutinib (160 mg, orally, twice daily) 3. Lenalidomide (15–25 mg, orally, d1–d21, repeat every 28 days) ± rituximab
	WM	TN/R/R: Ibrutinib (420 mg, orally, once daily) ± rituximab	
	FL	TN/R/R: Lenalidomide (20 mg, orally, d1–d21, repeat every 28 days) + rituximab	
	MZL	TN: Lenalidomide (20 mg, orally, d1–d21, repeat every 28 days) + rituximab	R/R: 1. Ibrutinib (560 mg, orally, once daily) 2. Lenalidomide (20 mg, orally, d1–d21, repeat every 28 days) + rituximab
Aggressive lymphoma	MCL	TN: No consensus	R/R: 1. Ibrutinib (560 mg, orally, once a day) ± rituximab 2. Lenalidomide (15–25 mg, orally, d1–d21, repeat every 28 days) + rituximab 3. Ibrutinib (560 mg, orally, once a day) + lenalidomide (15 mg, orally, once a day, d1–d21) + rituximab 4. Zanubrutinib (160 mg, orally, twice daily)
	DLBCL	TN: Ibrutinib (560 mg, orally, once daily) + R-CHOP	R/R: 1. Ibrutinib (560 mg, orally, once daily) 2. Lenalidomide (20–25 mg, orally, d1–d21, repeat every 28 days) + rituximab
	PCNSL	TN/R/R: Ibrutinib (560 mg, orally, once daily)	

^a Oral drugs and dosages in the table are derived from guidelines, consensus, and article recommendations [2–6,21,35,45,46,50].

maintenance therapies [54]. Patients who need emergency treatment still need to go to the hospital in time.

Some new targeted drugs might have a certain therapeutic or protective effect on COVID-19. Studies have shown that BTKis have some protective effects in the development of COVID-19. Some drugs might block the pro-inflammatory process and chemokines in the lung tissue and inhibit polarization from M1 to M2 in macrophages [55–57]. However, an international multicenter study on COVID-19 patients with CLL [58] showed that the use of BTKis during COVID-19 treatment did not affect survival. The efficacy of BTKis on COVID-19 patients with malignant hematological tumors still requires further clinical verification.

During treatment, follow-up can be conducted in a non-contact manner, such as in online clinics. At the same time, attention should be paid to the patient's psychological condition during treatment. Due to the impact of this epidemic on treatments, patients worry about the failure to obtain timely and effective treatment, and this phenomenon will lead to psychological issues. However, the problem can also be solved through online psychological counseling combined with offline treatment.

Oral drugs represented by BTKis remain a mainstay of treatment for BCL either as monotherapy or in combination with other drugs. Thus, the appropriate

management of oral agent-emergent toxicities is essential. The safety profile of BTKis (ibrutinib and zanubrutinib) and immunomodulators (lenalidomide) are generally acceptable, and the toxicities of these oral agents are manageable in registration trials. Most of the adverse events related to BTKis (ibrutinib and zanubrutinib) are mild (grade I/II), requiring only supportive treatment. A Chinese expert consensus has detailed the safety and adverse event management in long-term ibrutinib treatment [59]. Coutre *et al.* [60] showed that the long-term safety profile of ibrutinib mainly included grade 1/2 diarrhea and fatigue, while grade 3/4 neutropenia and pneumonia occurred in 18% and 12% of patients, respectively. The ASPEN trial (NCT03053440) showed that grade ≥ 3 adverse events were reported in 63% and 58% of ibrutinib and zanubrutinib patients, respectively; 41% and 40% of ibrutinib and zanubrutinib patients experienced at least one serious adverse event, respectively [34]. Neutropenia, thrombopenia, venous thromboembolism, rash, and second primary malignancies might emerge during lenalidomide-based treatment, requiring careful monitoring [61,62]. Drugs should be discontinued for patients with uncontrollable toxicities and changed to alternative agents. Furthermore, using BTKis (ibrutinib and zanubrutinib) concomitantly with strong and moderate CYP3A inhibitors or strong CYP3A inducers should be avoided, and ibrutinib should

not be given with warfarin concomitantly [3].

Overall, to maximize the safety and long-term tolerability of oral drugs for BCL, clinicians should carefully consider the clinical history of each patient, fully understand the symptoms of the adverse effects, appropriately inform the patients about the risk of adverse effects, use upfront educational initiatives to maximize patient self-reported early signs of adverse events, regularly monitor for side effects, and take appropriate and prompt interventions to minimize drug toxicity and avoid interruption of therapy.

Conclusions

This study reviewed the application of oral drugs in the treatment of BCL and the latest research and provided appropriate recommendations for oral drugs for BCL patients according to the Lymphocyte Disease Group, Chinese Society of Hematology, Chinese Medical Association. In the treatment of BCL, BTKis (represented by ibrutinib and other types of oral drugs) are widely used in clinical practice, especially in the context of the current global pandemic of COVID-19, due to their high accessibility, medical convenience, and reliable efficacy. With the deepening of research and the development of standardized clinical applications, oral medications will bring better treatment to BCL patients, enabling more patients to benefit from them.

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Compliance with ethics guidelines

Suning Chen, Weili Zhao, Jianyong Li, Depei Wu, and Lymphoid disease Group, Chinese Society of Hematology, Chinese Medical Association declare that they have no competing interests. This manuscript is a consensus and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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