Challenges associated with the use of Bruton's tyrosine kinase inhibitors: A life-saving therapy for chronic lymphocytic leukemia (Review)

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Abstract. The adverse effects (AEs) of chemotherapy for chronic lymphocytic leukemia (CLL) can currently be avoided using Bruton's tyrosine kinase inhibitors (BTKis) and/or B-cell leukemia/lymphoma 2 (BCL2) inhibitors, which have increased the efficacy of therapy and improved the prognosis of patients. The progression-free survival and overall response rate of patients are significantly longer with the use of BTKis compared with the use of combination therapy. They are standard of care for use as frontline therapy and for the treatment of refractory or relapsed CLL. The use of BTKis is also indicated for patients with active disease and del17p, TP53 mutation, or unmutated immunoglobulin heavy chain genes, for their greater efficacy compared to chemotherapy + anti-CD20 monoclonal antibodies or BCL2 inhibitors. Ibrutinib inhibits various specific immune receptors, exerts immunomodulatory effects, and some immune manifestations respond to ibrutinib. The main limitations associated with the use of BTKis are the following: The emergence of drug resistance, low complete remission rates, the need for an indefinite treatment duration and possible AEs. The use of ibrutinib is not recommended for patients with ventricular arrhythmias, and the use of any BTKi is not recommended for those with a history of heart failure. Patients who are intolerant to ibrutinib can receive a more selective BTKi. Patients who develop resistance to covalent BTKis can be treated with a non-covalent BTKi or with a BCL2 inhibitor. BTKis can be administered in combination with an anti-CD20 monoclonal antibody and/or a BCL2 inhibitor to reduce the proliferation of resistant clones, and sometimes to allow the shortening of the treatment duration. Further developments include Bruton's tyrosine kinase degraders, the combination of BTKis with immune checkpoint inhibitors or chimeric antigen receptor T-cells, or drugs that target 6,7-dimethoxy-N-(pyridin-3-yl) quinazolin-4-amine or actin cytoskeleton organization.

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Abbreviations: AEs, adverse effects; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; BCL2, B-cell leukemia/lymphoma 2; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; CRISPR, clustered regularly interspaced short palindromic repeats; Cas9, CRISPR-associated protein 9; CR, complete response; ncBTKis, non-covalent inhibitors of Bruton's tyrosine kinase; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, refractory or relapsed; TKis, tyrosine kinase inhibitors; uMRD, undetectable measurable residual disease

Key words: acalabrutinib, Bruton's tyrosine kinase inhibitors, chronic lymphocytic leukemia, ibrutinib, zanubrutinib

Contents

1. Introduction
2. Advantages associated with the use of Bruton's tyrosine kinase inhibitors
3. Immunomodulatory effects
4. Limitations of Bruton's tyrosine kinase inhibitors
5. Advantages associated with the use of non-covalent Bruton's tyrosine kinase inhibitors
6. Therapeutic combinations
7. Conclusions and future perspectives

1. Introduction

The median age of patients with chronic lymphocytic leukemia (CLL) is 70 years. As many of these patients are immunocompromised, they are thus prone to developing various infections. Of note, 70-80% of patients with CLL are asymptomatic at the time of diagnosis, and approximately one third of patients will never require treatment for CLL (1). The CLL-International Prognostic Index was validated as the optimal predictor of time to first therapy among previously untreated patients (2).

The most commonly indicated drugs currently available for first-line treatment are covalent Bruton's tyrosine kinase (BTK) inhibitors (BTKis) and B-cell leukemia/lymphoma 2 (BCL2) inhibitors (1). Moreover, they are currently the standard of care for use as frontline therapy and for the treatment of refractory or relapsed (R/R) CLL.

BTK is a member of the TEC-family non-receptor protein-tyrosine kinases and is involved in the proliferation

and differentiation of B-lymphocytes. The activation of BTK is the result of the activation of receptors, such as B-cell antigen receptor, C-X-C chemokine receptor type 4 and various integrins, including VLA-4. Once activated, BTK initiates trophic signals that contribute to prevent cell death, and promote cell activation and growth (3).

Ibrutinib was the first BTKi to be approved by the FDA, in 2013. It constitutes a turning point in CLL therapy as it allows for the avoidance of the toxicity associated with chemotherapy. Its success was considerable, including from a financial point of view (4). It is a potent, covalent, irreversible, selective inhibitor of BTK, which alters BTK-dependent adhesion and migration, which explains the disruption of the retention of CLL cells in the supporting lymphoid tissues. The relative expression of the receptors involved in lymph node entry (CCR7) vs. exit (S1PR1) represent markers of the clinically relevant treatment-produced lymphocytosis (5). Acalabrutinib and zanubrutinib are covalent and irreversible second-generation BTKis, which aimed at reducing off-target effects. They were approved in 2017 and 2019, respectively (4). Orelabrutinib is another novel next-generation, covalent and irreversible BTKi with a high selectivity for BTK that was approved in China and Japan for the treatment of R/R CLL in 2020 (6,7). Tirabrutinib, another covalent and irreversible BTKi, was approved in Japan, in 2020, for the treatment of recurrent or refractory primary central nervous system lymphoma (8). The FDA has granted an accelerated approval to pirtobrutinib, a non-covalent and reversible BTKi, as a therapy for adult patients with CLL who have been treated with at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor, in 2023 (9).

Both BTKis, as well as venetoclax (a BCL-2 inhibitor) and next-generation anti-CD20 monoclonal antibodies, have resulted in improved therapeutic results in patients with CLL, even in those with del17p13 or TP53 mutation and unmutated immunoglobulin heavy chain (IGHV) genes, which represent high-risk features (2). Although the venetoclax-obinutuzumab combination may be a limited treatment solution, a BTKi is indicated if patients have the del17p, TP53 mutation, or unmutated IGHV, as it has greater efficacy; in these cases, the combinations BTKi-venetoclax ± anti-CD20 monoclonal antibody also appear to be useful (10).

For patients with multiple relapses of CLL, chimeric antigen receptor T-cell (CAR-T) therapy with lisocabtagene maraleucel is a solution that leads to a 45% complete response (CR) rate. The allogeneic hematopoietic cell transplantation is the only potentially curative solution, after use of targeted agents, in selected patients (5).

The present review summarizes and discusses the efficacy and safety of BTKis in patients with CLL. Articles published in the PubMed and Web of Science databases between October, 2022 and September, 2023 were searched, using the terms 'chronic lymphocytic leukemia' and 'BTK inhibitors'.

2. Advantages associated with the use of Bruton's tyrosine kinase inhibitors

BTK plays a role in B-cell receptor (BCR) signaling (Fig. 1) (11): The binding of the antigen to the BCR leads to the phosphorylation of its co-receptors, CD79A and CD79B, by the recruited tyrosine kinases, LYN and SYK, thereby recruiting SYK. SYK activates Pl3Kδ, which converts PIP2 to PIP3. PIP3 constitutes a docking site for BTK. BTK phosphorylates and activates phospholipase C γ2 (PLCγ2), which is involved in the activation of protein kinase C (PKC)β. PKCβ phosphorylates IKK, which activates NF-κB, a nuclear factor involved in the gene expression necessary for B-lymphocyte survival and proliferation. BTK stimulates PLCγ2 lipase activity, which produces Ca^{2+} influx and nuclear factor of activated T-cell activation via CaM; this nuclear factor also regulates gene expression in lymphocytes. PLCγ2 is also involved in MYC (another nuclear factor) activation through the RAS/MEK1/2 and ERK1/2 pathway; MYC activates the expression of a number of proliferative genes.

The structure of BTK is presented in Fig. 2. The activation of BTK requires the phosphorylation of the Y551 and Y223 sites. The covalent BTKis have as their main target Cys481 residues on the catalytic domain (11).

The covalent BTKis are presented in Table I (4,12-18). Ibrutinib binds irreversibly to the BTK, decreasing the phosphorylation of this protein and thereby decreasing downstream BCR signaling, a pathway that plays a crucial role in the survival of CLL cells (19). The design of a covalent DNA-encoded library and its selection method was realized and published to facilitate the discovery of covalent inhibitors for target proteins, including BTK (20). BTKis allow for the avoidance of the adverse effects (AEs) of classical chemotherapy and their use has led to deeper responses, including in high-risk patient categories. Oral administration is another advantage of BTKis; however, the therapy is continued until the disease progresses or until discontinuation is required due to unacceptable toxicity (19).

The non-covalent BTKis (ncBTKis) are the following: Pirtobrutinib-a third-generation BTKi with a selectivity for BTK of >300-fold higher than >98% of other kinases, and a nanomolar potency against both wild-type and C481-mutant BTK (21). The following drugs that are at various stages of clinical testing: Nemtabrutinib (less selective than other ncBTKis) (11), vecabrutinib-a selective, reversible inhibitor of BTK, B-lymphocyte kinase, insulin-like growth factor 1 receptor, interleukin-2-inducible T-cell kinase (ITK), LCK and TEC, but not EGFR, with a potency against BTK with a half-maximal inhibitory concentration] (19) and fenebrutinib (a selective BTKi). The latter two drugs have been discontinued in B-cell malignancies (19), due to adverse effects. The results of clinical trials with BTKis are presented in Table II (13,22-27).

A recent meta-analysis included 1,510 patients treated for CLL/small lymphocytic lymphoma with BTKis or combination therapy. The progression-free survival (PFS) and overall response rate (ORR) were significantly longer for patients who received BTKis compared to the combination therapy, although the overall survival (OS) and CR rate did not differ between the two study arms (28). It has been shown that the survival rates of patients are ~88% at 4 years under acalabrutinib treatment, 94% at 2 years under zanubrutinib treatment and 78% at 7 years under ibrutinib treatment (1).

Covalent BTKis

Ibrutinib. The effectiveness of ibrutinib administered to naïve patients with CLL in real-world clinical settings was previously examined in a systematic literature review. The PFS rates

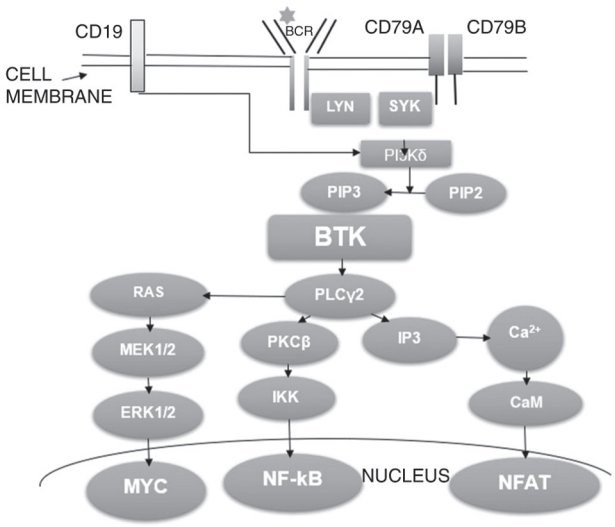

Figure 1. The mechanism of antigen-dependent B-cell receptor signal transduction. The figure was adapted and modified from the study by Alu *et al* (11) (https://creativecommons.org/publicdomain/zero/1.0/). BCR, B-cell receptor; LYN, LYN tyrosine kinase; SYK, spleen tyrosine kinase; Pl3Kδ, phosphoinositide 3-kinase δ; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; BTK, Bruton's tyrosine kinase; PLCγ2, phospholipase C γ2; RAS, signal transduction protein RAS; MEK, mitogen-activated kinase MEK; ERK, extracellular signal-regulated kinase; MYC, transcription factor MYC; PKCβ, protein kinase Cβ; IKK, IκB kinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B-cells; IP3, inositol 1,4,5-triphosphate; CAM, calmodulin; NFAT, nuclear factor of activated T-cells.

were between 89 and 93%, and the ORR was between 71 and 90% after a 1-year follow-up period. Following an 18-month follow-up period, the OS rate was 91%. These data support the high efficacy of ibrutinib in real-life (29). Other results of ibrutinib therapy are presented in Table II.

Following an 8-year follow-up, it was found that ibrutinib reduced all-cause mortality, and produced few cases of ventricular arrhythmias and sudden cardiac death, independently of QT lengthening (28). In the case that AEs occur, both the reduction of the dose of ibrutinib and the careful management of arrhythmia can allow for long-term treatment and reduce all-cause mortality with a prolonged PFS and a reduced all-cause mortality (30).

In a real-world retrospective analysis, it was found that ibrutinib had better efficacy and tolerability than the rituximab-idelalisib combination in patients with R/R CLL (31). It has been found that ibrutinib and venetoclax work synergistically and they have been proven to be effective in clinical trials (32).

In order to reduce the number of AEs associated with the use of ibrutinib, more specific inhibitors of BTK were produced; thus, acalabrutinib and zanubrutinib have equivalent/enhanced efficacy and improved tolerability (33).

Acalabrutinib. Acalabrutinib has been approved for CLL therapy and has an efficacy comparable to that of ibrutinib, although with fewer AEs (34). As a result, is was previously demonstrated that patients who received acalabrutinib had a 41% lower risk of discontinuation and a longer time to discontinuation compared to those treated with ibrutinib (35). Acalabrutinib monotherapy given in treatment-naïve patients with CLL was found to be cost-effective compared to chlorambucil + obinutuzumab (36). Acalabrutinib, unlike ibrutinib, does not inhibit anti-CD20 monoclonal antibody-dependent cellular phagocytosis; thus, its association with rituximab is suitable (37). As with acalabrutinib, its major metabolite, ACP-5862, is more selective towards BTK compared to ibrutinib and zanubrutinib. ACP-5862 is involved in the clinical efficacy of acalabrutinib treatment (38).

Zanubrutinib. Zanubrutinib, a BTKi with a greater specificity than ibrutinib, has been proven to be superior to it in terms of ORR in patients with R/R CLL (23). Zanubrutinib has a similar action to acalabrutinib, but is less active against ITK and TEC tyrosine kinase (39). It has been shown that zanubrutinib has excellent response rates and its approval is awaited. It produces fewer AEs, apart from high rates of neutropenia (34). Zanubrutinib has a lower risk of atrial fibrillation/flutter and major bleeding events (39). Zanubrutinib has been shown to significantly increase PFS vs. bendamustine-rituximab in first-line therapy (39,40).

Other covalent BTKis. Orelabrutinib is a highly selective covalent BTKi that targets a single kinase, BTK (41). Preclinical studies claim that orelabrutinib has a high selectivity, good efficacy and very good safety profile in B-cell lymphoproliferation (42). It has been proven to be effective and safe, including in Chinese patients with CLL (41).

Tirabrutinib is an irreversible and covalent BTKi. Administered in a Japanese study in patients with B-cell lymphoproliferations, it was shown to result in an ORR and a median duration of response of 76.5% and 2.59 years, respectively (43).

ncBTKis. ncBTKis have been produced to overcome resistance to BTKis; among the tested products, pirtobrutinib has been proven to be promising, with manageable toxicities (33).

Nemtabrutinib is a potent reversible BTKi of the new generation, effective in treatment-naïve and ibrutinib-refractory CLL cells *ex vivo*. In a previous study in a mouse model of CLL, the combination of nemtabrutinib and venetoclax led to longer survival rates vs. treatment with ibrutinib and venetoclax (32).

3. Immunomodulatory effects

BTKis inhibit various specific immune receptors, such as T-cell receptor and Toll-like receptors. As BTKis also inhibit other kinases, such as ITK, TEC and SRC family kinases, EGFR, they also affect the function of other cells, such as T-cells, natural killer cells, cardiomyocytes and platelets. These pathways explain the marked clinical efficacy of BTKis, but also their AEs, among which are infections, atrial fibrillation and bleeding (44).

Apart from the BTKi effect, ibrutinib is involved in suppressing the expression and trafficking of cytotoxic T-lymphocyte antigen 4, a key immune checkpoint and target for cancer immunotherapy. This is another immune benefit of ibrutinib (45).

T-lymphocyte responses following anti-SARS CoV-2 vaccination in patients with CLL occurred independently of the treatment status, although higher humoral response rates were observed in those under BTKi treatment and following

Table I. The covalent BTKis.

BTKi	Biochemical potency[a]	Selectivity	Inhibited targets
Ibrutinib	+++	+	TEC kinase, ITK, BTK and the subsequent phosphorylation of BTK, phospholipase Cγ2, AKT and ERK
Acalabrutinib	+	+++	BTK, BMX kinase, and human EGFR4; almost no inhibitory activity on EGFR, ITK, or TEC kinase
Zanubrutinib	++	++	BTK, BMX kinase, and human EGFR4; almost no inhibitory activity on EGFR; less activity on TEC and ITK
Orelabrutinib	+	+++	Significant inhibition only of BTK
Tirabrutinib	+	+++	BTK

[a]Based on biochemical binding kinetics. BTKi, Bruton's tyrosine kinase inhibitor; EGRF, epidermal growth factor receptor; ITK, IL2-inducible T-cell kinase.

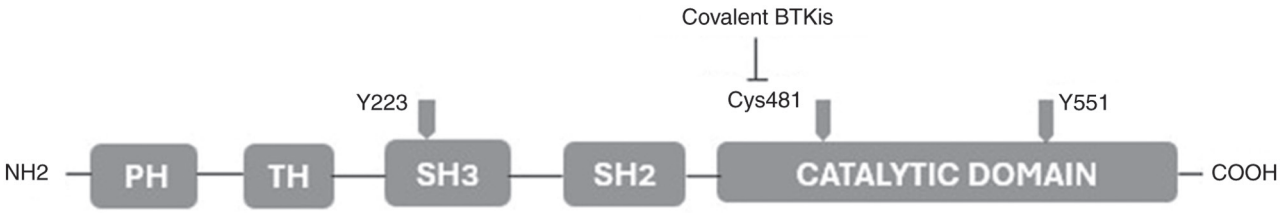

Figure 2. Structure of Bruton's tyrosine kinase. The figure was adapted and modified from the study by Alu *et al* (11) (https://creativecommons.org/publicdomain/zero/1.0/). PH, amino-terminal pleckstrin homology domain; TH, proline-rich TEC homology domain; SH3, SRC homology domains SH3; SH2, SRC homology domains SH2.

B-lymphocyte reconstitution. Boosting was more effective in patients with improved immunity by leukemia treatment (46).

In a previous study, ibrutinib was shown to be useful for the treatment of 25 patients with R/R B-cell lymphoma or leukemia and hematological immune manifestation; ~67% of the immune manifestations responded to ibrutinib; the CR rate was 44% (47).

4. Limitations of Bruton's tyrosine kinase inhibitors

The main limitations of BTIs are the following: The emergence of drug resistance, low complete remission rates, the need for an indefinite treatment duration (39) and the possible occurrence of AEs, which vary depending on the product, and can be responsible for intolerance.

The permanent discontinuation of BTKis within the first 6 months of their administration, most of the time due to progressive disease, has led to a median post-discontinuation survival of only 6.9 months (48).

The bioavailability of acalabrutinib from capsules decreases if proton-pump inhibitors are co-administered. However, tablets of acalabrutinib maleate with pH-independent release were produced, to avoid this limitation (49).

AEs. Some of the AEs of ibrutinib are due to the inhibition of kinases other than BTK (32). A recent meta-analysis found that the risk of developing grade ≥3 AEs did not differ significantly between patients treated with BTKis compared to those treated with combination therapy. Moreover, the risk of developing grade ≥3 AEs was significantly lower in the group of patients treated with second-generation BTKis compared to the combination therapy (28).

Hypophosphatemia can appear during treatment with tyrosine kinase inhibitors (TKis); it has the same mechanism that is involved in the production of secondary hyperparathyroidism and renal tubulopathy and can be managed with alternating doses of TKis (50).

Males are more prone to the occurrence of AEs during ibrutinib and acalabrutinib treatment (51). Ventricular arrhythmias and sudden cardiac death are a class effect of BTKis (29), as well as hypertension, atrial fibrillation, heart failure (52), bleeding (10) and gastrointestinal symptoms (50). Hypertension that occurs during treatment with ibrutinib has been proven to be reversible following the discontinuation of treatment. The factors associated with hypertension in these patients were the following: An older age, the male sex, tobacco use and chronic kidney disease. Baseline hypertension did not lead to major cardiovascular complications (53).

In accordance with the international consensus statement on the management of the cardiovascular risk of patients with CLL who are to be treated with BTKis, it is indicated to establish their cardiovascular diseases, risk factors and level, and perform the necessary investigations, including an electrocardiogram (52).

In the case that the patients have a high cardiovascular risk, it is indicated that a multidisciplinary team determines whether treatment with a BTKi is indicated: If the answer is positive, a selective BTKi (acalabrutinib or zanubrutinib) will be preferred. It is recommended to avoid the use of ibrutinib in patients with ventricular arrhythmias, and any BTKi in those

Table II. Clinical trials of BTKis.

The investigated drugs	Studied population	Results	Adverse effects	(Refs.)
Ibrutinib + rituximab/ FCR	771 Previously untreated patients with CLL	PFS at 53 months=non-reached with ibrutinib and rituximab, and 67 months in FCR group; OS was similar between groups	Grade 3 and 4 leukopenia-more frequent in the group treated with FCR; a small number of sudden unexplained or cardiac deaths was in the ibrutinib + rituximab group	(22)
Ibrutinib/zanubrutinib	652 Patients with relapsed or refractory CLL or SLL	PFS at 24 months=78.4% in the zanubrutinib group and 65.9% in the ibrutinib group; longer PFS in those with 17p deletion, a TP53 mutation, or both in the zanubrutinib group	Fewer cardiac events and adverse events that required treatment discontinuation in the zanubrutinib group	(23)
Zanubrutinib/ibrutinib	415 Patients with relapsed or refractory CLL	ORR at 15 months=78.3% in the zanubrutinib group and 62.5% in the ibrutinib group; PFS at 12 months= 94.9% with zanubrutinib and 84.0% with ibrutinib; ORR was higher with zanubrutinib vs. ibrutinib in patients with del(17p)/ TP53 mutations and del(11q)	Fewer patients had cardiac events (including the development of atrial fibrillation), major hemorrhages, and adverse events that required treatment discontinuation or leading to death in the zanubrutinib group	(24)
Pirtobrutinib	CLL or SLL including 247 patients previously treated with a BTKi	ORR=73.3%; median PFS= 19.6 months	The most frequent were infections, bleeding, and neutropenia; less frequently appeared: hypertension, atrial fibrillation or flutter, and major hemorrhage	(25)
Ibrutinib + autologous huCART-19	19 Patients with CLL without CR after ≥6 months of ibrutinib treatment	CR rate at 3 months=44%; the estimated OS and PFS at 48 months=84% and 70%, respectively; undetectable MRD at 12 months= 72% of tested patients	Cytokine release syndrome-in 15 of 18 subjects; neurotoxicity in 5 patients	(26)
Acalabrutinib/ investigator's choice	310 Patients with R/R CLL	PFS at 42 months=62% (acalabrutinib) vs. 19%; 42-month OS at 42 months= 78% (acalabrutinib) vs. 65%	During acalabrutinib treatment. Atrial fibrillation/flutter, 8%; hypertension, 8%; major hemorrhage, 3%' grade ≥3 infections, 29%; and second primary malignancies without non-melanoma skin cancer, 7%	(27)
Orelabrutinib	80 Patients with R/R CLL or SLL	ORR, 92.5%; CR=21.3%; PR=60.0%; PR with lymphocytosis 11.3%; high response rate also in the subgroup of patients with unfavorable prognostic risk	Approximately 86.8% of AEs were grade 1 or 2	(13)

BTKi, Bruton's tyrosine kinase inhibitor; AEs, adverse effects; CLL, chronic lymphocytic leukemia; CR, complete response; FCR, fludarabine, cyclophosphamide and rituximab; huCART-19, anti-CD19 chimeric antigen receptor T-cells with humanized binding domain; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; OS, overall survival; PFS, progression-free survival; R/R, refractory or relapsed; SLL, small lymphocytic lymphoma.

with a history of heart failure. The multidisciplinary team must contribute to the management of AEs that occur during BTKi therapy; thus, the control of hypertension, the therapy of arrhythmias and heart failure will help to maintain the therapy with BTKi (52).

The following AEs have been found to occur more frequently with ibrutinib than with acalabrutinib: Arthralgia, back pain, diarrhea, urinary tract infection, dyspepsia and muscle spasms, atrial fibrillation/flutter, hypertension, and bleeding. Instead, cough and headaches have been found to be more frequent with acalabrutinib (54).

Approximately a third of the B-lymphocytes of patients with CLL express CD73, the nucleotidase that produces adenosine. Adenosine 2A receptor activation leads to the amplification of the anti-platelet aggregation effect of ibrutinib (55).

In patients treated with ibrutinib, the first infection has been shown to occur after a median period of 125 days from the initiation of therapy. Risk factors for a severe infection are the following: Previous allogeneic hematopoietic stem cell transplantation and corticotherapy (56). The anti-infective prophylaxis of patients treated with BTKi should target opportunistic infections and it is indicated that it should be performed in collaboration with an infectious disease specialist (57).

The side-effects associated with the use of ibrutinib can be treated with supportive care or dose reduction, continuation with another covalent BTKi, or a ncBTKi, or another medication (58). Compared to ibrutinib, zanubrutinib has a better safety profile and an enhanced clinical efficacy, effects due to its higher selectivity for the kinase binding site (39). Acalabrutinib and zanubrutinib produce less episodes of atrial fibrillation, compared to ibrutinib (12).

As previously demonstrated, ~70% of the AEs that occurred during treatment with ibrutinib were not present with zanubrutinib treatment and ~80% of those that occurred during therapy with acalabrutinib did not recur with zanubrutinib (59).

Cardiovascular events have been found to occur less frequently in patients treated with zanubrutinib compared to those who received ibrutinib, although zanubrutinib produced a higher incidence of secondary cancers (60).

Among the main causes of mortality in patients treated with ibrutinib and acalabrutinib are infections, pneumonia, pleural effusion, diarrhea and fall. Cardiac disorders, such as atrial fibrillation and cardiac failure, are an important cause of mortality among those treated with ibrutinib (49).

Zanubrutinib has been shown to attenuate bleomycin-induced lung fibrosis in an experimental model in mice, by inhibiting the TGF-β1 signaling mechanism (61).

Resistance to BTKis. Resistance to BTKis can be primary or acquired, and can occur due to various mechanisms, such as gene mutations, the activation of bypass signaling mechanisms and the influence of the tumor microenvironment (12).

It is considered that the most common mechanism involved in the emergence of resistance to covalent BTKis (including ibrutinib), under which the disease progresses, is a mutation in the BTK 481 cysteine, a residue to which the inhibitors bind covalently (62,63). A high CD27 and CD86 expression associated with BTKC481S mutation has been found in patients with CLL resistant to ibrutinib. A higher expression of CD27, CD69 and CD86 has been found 3 months prior to the appearance of clinical resistance. Monitoring these phenotypic markers using flow cytometry could be useful to detect ibrutinib resistance (64).

Point mutations of the phospholipase *C-γ2* gene, such as *R665W* are other causes of resistance to BTKis (65) and progressive disease. Mutations in *BTK*, *PLCG2* or both genes are rare before any treatment for CLL (3, 2 and 1% of patients, respectively). Under treatment with ibrutinib, following a median follow-up of 35 months, in patients who did not have progressive disease at last sample, it was found that there were mutations in *BTK* (30%), *PLCG2* (7%), or both genes (5%), particularly in patients with R/R CLL (66).

BTK Leu528Trp mutation was observed in some patients treated with zanubrutinib and proved cross-resistance to pirtobrutinib, a non-covalent inhibitor (62). Homogeneous and bimodal CD49d-positive CLL cells have been shown to have a shorter time to progression (6.6 years) compared to homogeneously CD49d-CLL cells. During acalabrutinib therapy, signaling through NF-κB and JAK/STAT increases, as well as the adhesion, survival and migratory capacity of $CD49d^+$ CLL cells (67). CD49d remains activated despite therapy with ibrutinib or acalabrutinib, and can be attenuated by PI3K inhibitors (68). CD49d/VLA-4 expression is a contributing factor to BTKi resistance (67).

5. Advantages associated with the use of non-covalent Bruton's tyrosine kinase inhibitors

ncBTKis have a different mechanism of binding to BTK (32). They reversibly bind the BTK target, a fact that explains the rare occurrence of toxicity and acquired resistance (19). Their use is associated with fewer AEs than the covalent BTKis, and they have shown promising efficacy and safety profiles in clinical trials (44). Furthermore, they have the potential to overcome resistance of CLL cells due to mutations (32).

Pirtobrutinib is a ncBTKi that ensures high response rates in CLL cases that are refractory to covalent BTKis, regardless of the mechanism of this resistance (69). Pirtobrutinib potently inhibits cell viability, BCR signaling, and CCL3/CCL4 chemokine production, not only in BTK wild-type, but also in C481S-mutant CLL cells (63).

Pirtobrutinib has been shown to result in an ORR >70% following the failure of covalent BTKis and venetoclax (1,19). Early studies with pirtobrutinib found that it has a safety profile that can recommend it for use in therapeutic combinations (69).

The acquired resistance to pirtobrutinib has been recently observed; the mechanisms can include a novel acquired mutations in BTK outside of the C481 position (19,63).

6. Therapeutic combinations

The longer the treatment duration, the lower the response rate of CLL cells to the treatment, particularly if it is represented by a BTKi. Therefore, therapeutic combinations have been tested. In addition, they often have a synergistic effect, contribute to the reduction of the proliferation of resistant clones, and sometimes allow for the treatment duration to be shortened, with the reduction of AEs and costs (70).

A recent meta-analysis established the superiority of the combination of anti-CD20 monoclonal antibodies + BTKi or BCL2i compared to chemotherapy in the first-line treatment of CLL (71).

Another systematic review and meta-analysis evaluated four clinical trials with patients with treatment-naïve or R/R CLL and concluded that BTKis administered in combination with anti-CD20 antibodies led to the prolongation of PFS and ORR, but not OS and CR compared with chemoimmunotherapy. The risk of severe AEs induced by the two types of treatment was comparable (72). The addition of anti-CD20 monoclonal antibodies to BTKi therapy was compared to BTKi monotherapy in another systematic review and meta-analysis; PFS was significantly improved in the first group, as well as the CR and undetectable minimal residual disease rate, but not the OS; the risk of severe AEs was comparable in the two groups (73).

As previously demonstrated, the combination obinutuzumab-acalabrutinib was able to produce longer PFS compared to acalabrutinib, but this fact was not observed with the combination rituximab-ibrutinib; in addition, the AEs may be more important (10).

It has been shown that ibrutinib is able to produce deep responses in combination with venetoclax (74). The combined treatment with ibrutinib-venetoclax is more cytotoxic against CLL cells than any of the drugs used alone (75). The combination of BTKis with BCL-2 antagonists can be tested with the aim of increasing the anti-leukemic efficacy and reducing the risk of acquired resistance (16). In a previous study, patients with R/R CLL, who did not obtain undetectable measurable residual disease (uMRD) with venetoclax monotherapy at cycle 12 day 1, were treated with ibrutinib and both drugs were continued. Following a median of 7 months of combined treatment, 84% of patients achieved uMRD ($<10^{-4}$) and treatment was terminated; 2 patients with minimal residual disease continued ibrutinib until progression or toxicity (74).

In another study, the triple combination of BTKi-venetoclax-anti-CD20 monoclonal antibody led to similar rates of CR compared to the venetoclax-obinutuzumab combination, although with more potential AEs (3).

The broad involvement of BTK in immunological mechanisms, and particularly the influence of ibrutinib on T-lymphocytes, is a reason to combine BTKis with specific immunotherapies, such as immune checkpoint inhibitors, including the programmed cell death-ligand 1 (PD-L1) inhibitors, CAR-T therapy, or bispecific antibodies (BiAbs), particularly as a therapeutic solution for R/R diseases (44). However, it is known that the inhibition of BTK with a BTKi produces changes in immune cell numbers. It appears that the decrease in the number of T-cells occurs in parallel with the receding tumor burden. It is explainable why patients with R/R CLL have higher T-lymphocyte numbers than untreated and non-progressive patients. Combining ibrutinib with PD-L1 inhibitors has a synergistic effect compared to PD-L1 inhibition alone in experimental models of lymphoma. Clinical trials have found that the activity of the combination of nivolumab or pembrolizumab with ibrutinib is limited in CLL cells, but it is promising in patients with Richter transformation. BTK appears to be expressed in effector/memory T-cells and plays a key role in T-cell activation; thus, BTKis can target this mechanism (44). It has been established that ibrutinib is a clinically relevant and physiologically potent inhibitor of ITK (18,44). By inhibiting ITK, it decreases Th2 and Th17 cell numbers and potentiates Th1-based immune responses. The specific advantage given to Th1 lymphocytes may allow for the effective generation of antitumor immunity (18). Acalabrutinib and zanubrutinib have a weak effect on ITK and, as a result, do not alter the Th1/Th2 cell numbers (44).

Pre-treatment with ibrutinib before leukapheresis can reverse T-cell dysfunction and improve CAR-T cell production, which may be used as a bridging therapy before CAR-T cell therapy. Furthermore, ibrutinib or acalabrutinib, together with CAR-T cell therapy, can increase the number and function of T-lymphocytes, contributing to the increase in the engraftment and expansion of CAR-T cells, improving the anti-leukemic efficacy of CAR-T cells, and decreasing cytokine release syndrome in patients with CLL (44).

BiAbs, such as CD19/CD3-BsAb, recruit autologous T-cell cytotoxicity against CLL cells *in vitro*. Broad-spectrum BTKis can acutely abrogate the cytotoxicity of T-cell-directed BiAbs and CAR T-cells *in vitro* (76). Acute exposure to BTKis impairs T-cell activation and the lysis of target cells upon treatment with CD3-directed BiAbs, through an effect independent of BTK inhibition. This acute effect may be compensated in CLL, due to the direct toxicity of BTKis to tumor cells. T-lymphocytes from ibrutinib-treated patients have a greater *in vitro* antitumor efficacy than T-lymphocytes from ibrutinib-naïve patients when combined with BiAbs (76). It was demonstrated that T-lymphocytes from these patients expanded more rapidly and had superior cytotoxic activity in response to the BiAbs. BTKis enhance BiAb-induced cytotoxicity by relieving T-lymphocytes of immunosuppressive restraints imposed by CLL cells (77).

7. Conclusions and future perspectives

BTKis have contributed to improving the therapeutic results of patients with newly diagnosed or R/R CLL, for which they have become the standard of care. PFS and ORR are significantly longer with BTKis compared to the classical chemotherapy. BTKis are also indicated for patients with an unfavorable prognosis.

Ibrutinib has immunomodulatory properties, and selective BTKis have advantages compared to ibrutinib: An improved PFS or ORR, and produce fewer AEs (particularly cardiac events and adverse events that require treatment discontinuation).

The use of ibrutinib is not recommended for patients with ventricular arrhythmias, and the use of any BTKi is not recommended in those with a history of heart failure. A multidisciplinary team must contribute to the management of AEs that occur during BTKi therapy.

The combination of BTKis with an anti-CD20 monoclonal antibody and/or a BCL2 inhibitor aims at reducing the proliferation of resistant clones, and sometimes allows for the shortening of treatment duration. Studies using the combination of zanubrutinib with venetoclax, obinutuzumab and other drugs are underway (39). The combinations of BTKi and venetoclax have been proven to be well-tolerated and able to induce deep remissions (78).

The use of a ncBTKi or BCL2 inhibitor is a solution for patients who develop resistance to covalent BTKis. Patients with acquired resistance to BTKis could be treated with novel agents, such as BTK degraders [which act by ubiquitination and proteasomal degradation (32)], BiAb therapy, CAR T-cell therapy, PKCβ inhibitors, or various combinations (e.g., pirtobrutinib and venetoclax) that may contribute to overcoming this acquired resistance (19). BTK degraders function by removing BTK and could remain efficacious independent of BTK resistance mutations (79).

Due to the numerous immunological pathways in which BTKis are involved, their combination with other immunotherapeutic agents, such as immune checkpoint inhibitors or CAR-T-cell therapy, for the treatment of patients with relapsed or refractory CLL is under discussion (44).

A synthetic chemical product, 6,7-dimethoxy-N-(pyridin-3-yl)quinazolin-4-amine, was found through the screening of a large chemical library; it can serve as an effective molecular core from which various druggable dual inhibitors of the wild-type BTK and the C481S mutant would be produced (80).

Integrin-mediated homing and the retention of the malignant B-lymphocytes in the lymphoid organs can be achieved with the use of ibrutinib. However, there are patients with CLL intrinsically resistant to ibrutinib or who develop resistance to this drug (81). The clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein 9 (Cas9) system has been used in recent years for gene insertions or deletions into the genome of eukaryotic cells (82). An unbiased screening method uses functional genomic CRISPR-Cas9 to identify novel proteins involved in B-lymphocyte receptor-controlled integrin-mediated adhesion; these proteins can represent novel therapeutic targets to overcome ibrutinib resistance (81).

Actomyosin complex organization and altered mechanical properties of CLL cells may be involved in a novel mechanism of drug resistance. BTKis are able to restore the mechanical properties of the CLL cells to a healthy phenotype and are involved in actomyosin complex activation. Actin cytoskeleton organization could be a novel potential therapeutic target in CLL (83).

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Authors' contributions

RGM contributed to the preparation and design of the manuscript, drafting and editing the manuscript, and in the design of the tables. The author has read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The author declares that he has no competing interests.

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