The difference of Ibrutinib, Acalabrutinib and Zanubrutinib of BTK inhibitors for the treatment of B cell malignancies

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Abstract: Bruton's tyrosine kinase (BTK) inhibitor is a new drug with the potential to be highly effective in B-cell malignancies. A 68 percent response rate was observed in 111 individuals with relapsed or refractory mantle-cell lymphoma in a phase 1 study of ibrutinib. However, atrial fibrillation, bleeding, hypertension, and diarrhea are found the ASPEN Phase III clinical study of Ibrutinib so that many patients discontinue treatment. Zanubritinib and acalabrutinib which are the 2nd generation BTK inhibitors shows higher safety and fewer off-target effects. Nowadays, while BTK inhibition is highly effective as a single agent therapy, side effects may occur, spurring the development of combination medicines that increase clinical outcomes. In this review, different therapies including mono-therapy and combination therapies will be analyzed. Mono-therapy comparison of first-generation BTK inhibitor ibrutinib and second-generation Zanubritinib in Waldenstroms macroglobulinemia (WM), Chronic lymphocytic leukemia (CLL) and Mantle Cell Lymphoma (MCL) should be analyzed. Some examples would be administered in conjunction with ibrutinib, acalabrutinib, and abietinic combination therapy in CLL and MCL.

1. Introduction

According to Fisher [1], every year, round 20 new instances of lymphoma are diagnosed per 100,000 people in the Western world. Around 95% of lymphomas are B-cell malignancies, the remainder are T-cell malignancies. Bruton's tyrosine kinase (BTK) is one of the largest members of Tec family kinases in mammals and it is a key component of the B-cell receptor signaling pathway which regulates B cell proliferation and survival [2]. Currently, BTK inhibitors are one of the most effective treatment options recommended for lymphoma patients. A 68 percent response rate was observed in 111 individuals with relapsed or refractory mantle-cell lymphoma in a phase 1 study of ibrutinib [3]. Before BTK inhibitors were available, doctors often used chemotherapy to treat lymphoma. However, chemotherapy can have a variety of adverse effects. While it is destroying tumor cells, it is also destroying normal human cells. Some toxic effects and adverse reactions may occur with this treatment including damaged liver cells in varying degrees, diarrhea and suppress the bone marrow hematopoietic system [4]. Consequently, BTK has revolutionized the therapy landscape with chronic lymphoblastic leukemia (CLL) and has created new possibilities for the treatment of B cell malignant tumors.

Some researches shows that Immune cells such as B cells, mast cells, and macrophages are known to express BTK [2]. Additionally, an inhibitor of BTK is a promising new drug with potential efficacy in B-cell malignancies. B cell malignancies, such as mantle cell lymphoma (MCL), CLL, acute myeloid leukemia (AML), and activated B cell diffuse large B cell lymphoma, have a variety of aberrant expressions of BTK. Therefore, BTK inhibition is a critical area of study for the treatment of B-cell malignancies and immunological disorders involving B cells. After the first generation of BTK inhibitors ibrutinib was approved in 2013 in the U.S.A., BTK targeted therapy has gradually replaced traditional chemotherapy [5]. Currently, numerous BTK inhibitors are now approved by FDA. This review aims to give a brief comparison between the first-generation and second-generation BTK inhibitors in different therapies in the same disease. As well as comparing the effects of monotherapy and combination therapy of Ibrutinib, zanubrutinib and acalabrutinib in the same disease including MCL and CLL.

2. Comparison of the efficacy of Ibrutinib, Acalabrutinib and Zanubrutinib

2.1 Comparison of curative effect on WM

The ASPEN Phase III clinical trial (NCT03053440) compares Zanubrutinib to Ibrutinib in the treatment of relapsed/refractory (R/R) and newly treated (TN) WM patients [6]. The trial's major goal is to validate Zanubrutinib's superiority over ibrutinib by measuring complete remission (CR) or very good partial remission (VGPR) (VGPR). The primary response rate, duration of response, progression-free survival, and safety are among the trial's secondary objectives (determined by the incidence, time, and severity of adverse events during treatment). All patients (n=201) and R/R patients (n=164) were included in the trial's pre-determined analysis patient set. A measure of quality of life is included in the exploratory endpoint.

Based on the revised remission criteria [7] of the Sixth International Symposium on WM (IWWM-6), among the overall intention-to-treat (ITT) population, the sum of complete remission (CR) and very good partial response (VGPR) rates was 28% (95% CI: 20, 38), compared to 19% (95% CI: 12, 28) in the Ibrutinib group. Although the difference did not reach statistical significance, Zanubrutinib did show higher VGPR rate data and eased the trend of quality improvement.

In the ASPEN trial [6], Zanubrutinib showed better safety characteristics than Ibrutinib, and the incidence of specific adverse reactions related to BTK inhibitors was lower, including atrial fibrillation/atrial flutter (2% vs. 15 %), minor bleeding (49% vs. 59%) and major bleeding (6% vs. 9%). Although the incidence of grade 3 and above neutropenia is higher, compared with ibrutinib, there is no higher incidence of infection in patients treated with Zanubrutinib. Among the 101 WM patients treated by Zanubrutinib, 4% of the patients discontinued treatment due to adverse events, and 14% of the patients were dose-reduced due to adverse events.

In a word, the result shows that the 2nd BTK inhibitor, Zanubrutinib, which has better treatment tolerance than the treatment tolerance of the 1st one, Ibrutinib. Zanubrutinib may has superior curative effect than Ibrutinib's [6, 8, 9].

2.2 Comparison of curative effect on CLL

As for the clinical trials (Figure 1), nowadays, the 2nd generation of BTK inhibitors- Acalabrutinib and Zanubrutinib, are already available for clinical use, and other drugs are being studied [10]. These two drugs showed less inhibition of off-target kinases and increased BTK selectivity, as can be seen from their KINOME and IC50 values for off-target kinases.

Patients with R/R CLL (n = 85) received ibrutinib at a daily dose of 420 mg (n = 51) or 840 mg (n = 34) in the first Phase I/II research, and the ORR, defined as attaining a partial response (PR) or better, was identical at 71 percent for patients at each dose [11]. A PR with lymphocytosis (PR-L) was found in an additional 20% and 15% of patients in the two dosage groups, respectively [12]. Clinical and genetic risk factors, including del[17p] status, had no effect on the responses seen. The predicted PFS rate was 75 percent at 26 months, while the OS rate was 83 percent.

The efficacy of Zanubrutinib monotherapy in 78 individuals with CLL/SLL was evaluated in the Phase I BGB-3111-AU-003 study [10]. The ORR by investigator was 96.2 percent (75/78) (95 percent CI: 89.2–99.2) after a median follow-up of 13.7 months (range: 0.4–30.5 months), including two patients (2.6 percent) with a CR, 63 (80.8%) had a partial response, and ten (12.8%) had a PR-L. All 22 treatment-naive CLL/SLL patients had one CR, 18 PR, and three PR-L responses. Furthermore, all patients with a del[17p] or TP53 mutation who are efficacy-evaluable react [10]. Zanubrutinib's safety profile was excellent, with few off-target symptoms like as diarrhea and rash (seen in just 20% of patients and all grade 1 or 2 events), in keeping with the drug's strong selectivity for BTK inhibition.

Both trials indicated that Zanubrutinib's increased BTK selectivity is associated with fewer toxicities while maintaining the same efficacy.

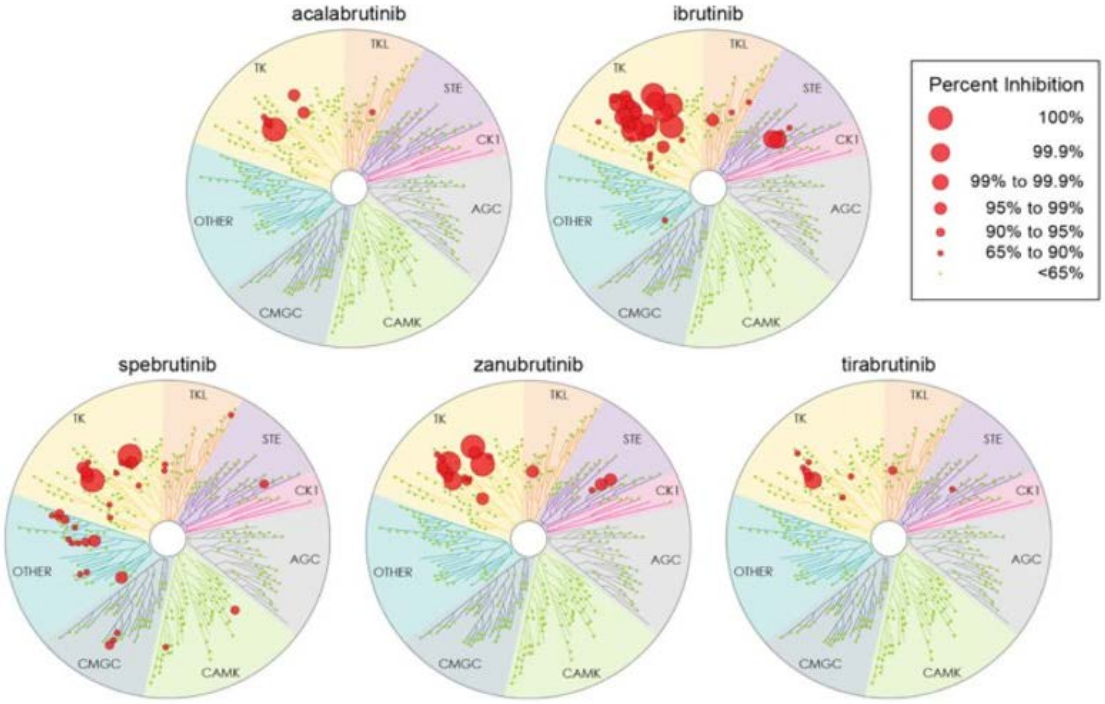

Figure 1. Kinome profiling of Bruton tyrosine kinase inhibitors.

2.3 Comparison of curative effect on MCL

The summary of pivotal studies of BTK inhibitors in patients with MCL is shown in table 1[13]. In PCYC-1104-CA, ACE-LY-004, and BGB-3111-206, responses were examined using computed tomography (CT) and/or positron emission tomography (PET)-CT (with PET-CT essential for confirmation of a complete response), and CT in BGB-3111-AU-003. MCL3001's response assessment technique was not specified. There are 11 patients with treatment-naive MCL in this study. Patients with relapsed/refractory MCL are reported to have the best outcomes.

Table 1. the summary of pivotal studies of BTK inhibitors in patients with MCL

BTK inhibitor	Study	n	Baseline Characteristic					Follow-up Median(months)	Outcomes			
			age	Intermediate/high risk by MIPI	Biastoid	# Of Prior therapies, Median (Range)	Refractory to last Therapy		ORR(CR)	Median(months)		
										DOR	PFS	OS
Ibrutinib	PCYC-1104-CA	111	68	38%/49%	15%	3(1-5)	45%	27	68%(21%)	18	13	23
	MCL3001	139	67	47%/22%	12%	2(1-9)	26%	39	77%(23%)	23	16	30
Acalabrutinib	ACE-LY-004	124	68	44%/17%	NA	2(1-5)	24%	26	84%(43%)	26	20	NR
Zanubrutinib	BGB-3111-AU-003	48	71	38%/38%	NA	1(1-4)	NA	15	87%(30%)	15	NA	NA
	BGB-3111-206	86	61	84% by MIPIb	14%	2(1-4)	52%	14	85%(77%)	14	17	NA

Note: Abbreviations: CR, complete response; DOR, duration of response; MIPIb, biological Mantle Cell Lymphoma Prognostic Index (MIPI); NA, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; sMIPI, simplified MIPI.

The result of table 1 shows that the ORR of Zanubrutinib (87% and 85%) and Acalabrutinib (81%) are both higher than the ORR of Ibrutinib (68% and 77%). What's more, the CR of Acalabrutinib (43%) and Zanubrutinib (30% and 77%) are higher than the one of Ibrutinib (21% and 23%), which demonstrates the 2nd BTK inhibitor Acalabrutinib and Zanubrutinib are more effective.

3. Combination Therapy of BTK inhibitor in B-cell malignancies

After BTK resistance, most medications fail to provide a long-term response, making combination studies of BTK inhibitors less valuable than trials of other inhibitors. Preliminary results from these investigations, however, will support the need for well-designed randomized and larger clinical trials to confirm that some medications should be used in combination rather than as a single agent.

3.1 Chronic Lymphocytic Leukemia

3.1.1 Ibrutinib

In fact, combination therapy in CLL with ibrutinib cannot be seen as an effective means compared with monotherapy until now. In fact, combination therapy in CLL with ibrutinib cannot be seen as an effective means compared with monotherapy until now. R/R CLL patients with high risk of relapse responded well to ublituximab which is a new anti-CD20 monoclonal antibody, as did Sharman JP [13] (17p deletion, TP53 mutation, or both). One group had a higher ORR (83% vs. 65%; P=0.02), while the other saw an increase in PFS (HR, 046; 95% CI, 024–087; P=0.016); however, there actually was similar in OS between the two groups. UMRD rates, encompassing bone marrow, peripheral blood or both (42% vs 6%; $P < 0.001$), were detected more frequently in combination with ibrutinib than in the absence of the drug. Anti-CD20 ublituximab was used long-term in this experiment, unlike most other trials when it was given for only six months. Toxicities such as infusion reactions (49% vs 3%), neutropenia (19% vs 12%), and atrial fibrillation (7% vs 2%) were more common in the combination arm. Also in the combination arm, the use of growth factors was increased with 15 % vs 9 %. The trial of COG-ACRIN E1912 [14] compared ibrutinib and rituximab

to chemotherapy (FCR is fludarabine, cyclophosphamide and rituximab) in healthy, untreated CLL patients aged less than or equal to 70 who did not show evidence of 17p deletion. Patients who were in the ibrutinib + rituximab group had statistically significant improvements in OS (98.8% vs 91.5 %; $P < 0.001$) and PFS (89.4% vs 72.9%; $P < 0.001$) after a median follow-up of 33 months, according to the data. Patients with IGHV mutations were divided into designated subgroups for analysis, treatment with ibrutinib + rituximab (87 %) and chemotherapy (chemoimmunotherapy) did not vary statistically in terms of PFS after three years (88%). Ibrutinib alone, ibrutinib + rituximab, and bendamustine + rituximab was all tested in the ALLIANCE A041202 [15] in a distinct cohort of untreated CLL patients (65 years old and above). Bendamustine plus rituximab patients who experienced illness progression were allowed to transition to the ibrutinib treatment arm. Ibrutinib alone (87%) and ibrutinib+rituximab (88%) groups exhibited significantly longer progression-free survival (PFS) than the bendamustine+rituximab arm (74%) at two years. However, after 38 months of follow-up, there was no significant difference in OS between the two groups. Ibrutinib monotherapy and ibrutinib plus rituximab did not differ substantially in PFS (HR, 1.00; 95% CI, 0.62–1.62; $P = 0.49$). Overall, these studies support the use of ibrutinib in combination therapy for patients with unidentified benefits or adverse effects, and in the future, the majority of untreated CLL patients will be treated with innovative drugs. Ibrutinib should be monitored for longer periods of time to validate these findings and improve its efficacy.

3.1.2 Acalabrutinib

Acalabrutinib is an appealing alternative to ibrutinib, which has more long-period follow-up data. A higher safety profile with decreased incidence rates of hypertension and atrial fibrillation is provided by Ibrutinib when compared. As a result, the combination of acalabrutinib, Obinutuzumab, and venetoclax in 24 treatment-naive patients with CLL was recently presented with promising results [16]. The bone marrow MRD clearance rate in this study was 50% (sensitivity 10–4), and all patients reacted. This triplet vs doublet combo therapy is now being investigated in several active clinical trials (NCT03836261, NCT03580928, and NCT04169737). As a result, the curative impact of acalabrutinib combination therapy in the treatment of CLL is still being investigated.

3.1.3 Zanubrutinib

The curative impact of zanubrutinib in combination therapy is dependent on the drug combination. Patients with B-cell malignancies who received zanubrutinib and tislelizumab in a phase Ib trial showed promising therapeutic efficacy. Side effects such as upper respiratory tract infections (51%) and neutropenia (44%), which were still the most common, tend to occur more frequently when Obinutuzumab is combined with the CD20-antibody [17]. Patients with tn CLL had a general response rate (ORR) of 100%, while those with R/R CLL had an ORR rate of 92.9%. The median follow-up period was 29 months. Venetoclax was evaluated in 39 individuals with tn CLL in a phase 2 study [18]. UMRD levels in peripheral blood (PB) and bone marrow (BM) were measured in this study. With no extra safety concerns, the combination of Obinutuzumab, venetoclax and zanubrutinib led to uMRD in 68 % of PB patients and 51 % of BM patients. In a phase Ib trial (NCT02795182) [19], zanubrutinib plus tislelizumab demonstrated encouraging clinical activity in patients who got B-cell malignancies. Therefore, Obinutuzumab cannot be added solely in zanubrutinib, but with venetoclax. And combining it with tislelizumab has already proven to be a successful treatment.

3.2 Mantle Cell Lymphoma

3.2.1 Ibrutinib

In MCL, there is already some accessible therapeutic regimen with various medicines for combination therapy with ibrutinib. In preclinical models of MCL [20], venetoclax and ibrutinib increased dephosphorylation of BTK substrates and lowered antiapoptotic BCL2 family members. Venetoclax was increased to 400 mg in a phase II study (AIM study) of MCL relapsed/refractory patients after an initial ibrutinib lead-in period of one cycle [21]. Patients with relapsed or refractory MCL who had CT and PET scans revealed 42% and 62%, respectively, of CR rates. Using flow

cytometry and PCR, MRD testing indicated a positive frequency of in the bone marrow (67 %) and the blood (38 %). It was revealed at the ASH 2019 conference [22] that after a median follow-up of 37.5 months, the median PFS and OS for this experiment were 29 and 32 months, respectively. Overall survival (OS) at 22.5 months, which is longer than the 22.5 months reported in an earlier trial in which 55% of patients with TP53 mutations had a response lasting at least 24 months, was also higher than the 22.5 months reported in that study. There may be people who benefit from the combination of Ibrutinib with venetoclax therapy even if they have TP53 mutations. A short course of treatment may even lead to long-term remission in certain patients, which is even more exciting. Ibrutinib/venetoclax versus ibrutinib alone will be tested in the phase III SYMPATICO trial (NCT03112174), which currently has patients enrolling. Because of the positive results of the prior tests, the combination of Obinutuzumab/ibrutinib/venetoclax is being tested in the ongoing OASIS study [23]. Patients with relapsed or refractory MCL (n = 9, 2 with blastoid MCL) treated with Obinutuzumab and ibrutinib for six cycles were found to be in 87% complete remission (CR) and 67 % MRD-negative by PCR in their blood and bone marrow in four of six patients. There was a worsening of the illness in four of the 12 patients who received the first two cycles of Obinutuzumab with ibrutinib and venetoclax (n = 12, 4 with blastoid MCL). Remission was confirmed in five of the nine patients who completed cycle 6 testing, however the MRD analysis is still ongoing. In this exploratory study, Obinutuzumab/venetoclax/ibrutinib appears to be safe and effective in the treatment of relapsed/refractory MCL [23], but bigger trials are needed to evaluate whether this combination is more successful than individual medications or two-medicine combinations.

3.2.2 Acalabrutinib

BTK inhibition in combination with immunotherapy was shown to be potentially effective in the studies described above. A BTK inhibitor, acalabrutinib, was also evaluated as a viable combo treatment option. However, an NCT02972840 study [24] is examining whether or whether it is possible to use the combination of BR and acalabrutinib. Patients with MCL who have never had treatment or who have relapsed/refractory MCL are also being studied with the combination of venetoclax, acalibrutinib, and rituximab (NCT02717624) [23]. A long-term study of the acalabrutinib combination is now underway.

4. Conclusion

To sum up, BTK inhibitors is a major area of investigation for the treatment of B-cell malignancies and immunological diseases involving B cells. According to previous research, when compared to ibrutinib, zanubrutinib had a lower rate of adverse events in atrial fibrillation, hemorrhage, hypertension, and diarrhea during WM therapy. In therapy of CLL, it showed that the second-generation drugs including Acalabrutinib and Zanubrutinib were less inhibition of off-target than Ibrutinib and the selectivity of them was increasing. Also, the 2nd generation drugs are less toxic which means that 2nd generation monotherapy is safer. Both monotherapy of ibrutinib and the combination of ibrutinib with rituximab showed the similar curative effect. However, both treatments are more effective than the combination of bendamustine with rituximab. In therapy of MCL, it showed that both zanubritinib and acalabrutinib were less off-target and toxic especially cardiovascular toxicity than ibrutinib. Furthermore, in comparison with combined therapy, there is still a lack of durable responses with therapies. Up to now combination therapy with ibrutinib is not particularly effective in this disease. Especially compared to ibrutinib alone with bendamustine plus rituximab and ibrutinib plus rituximab, PFS between ibrutinib alone and ibrutinib plus rituximab is similar even higher than the other control group. Obinutuzumab combines with venetoclax and tislelizumab as an effective therapy because of well tolerated. Other therapies in this review shows adverse events including upper respiratory tract infections and neutropenia. In therapy of MCL, many experiments show obinutuzumab/venetoclax/ibrutinib combination may be safe. As for the acalabrutinib combining, the experiment is still ongoing. To give a further research question, the incidence of neutropenia is higher in the 2nd generation BTK inhibitors that the safety of the drug

deserves further study. Toxicity, costs, and efficacy should be balanced when determining a drug combination strategy. Longer follow-up is needed to improve these methods.

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