Molecular Management of Chronic Lymphocytic Leukemia:
Towards a Chemotherapy-Free Approach

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ABSTRACT

B-cell receptor (BCR) signaling is implicated as a pivotal pathway in tumorigenesis in B-cell malignancies. The inhibitors of Bruton's tyrosine kinase (BTK) and phosphatidylinositide 3-kinase-delta (PI3K), modulating BCR signaling, have included into the clinical studies and demonstrated high response rates in B-cell lymphoproliferative diseases such as chronic lymphocytic leukemia (CLL). The imbalance between proliferation and apoptosis is the novel target in the treatment of CLL. The newly developed targeted molecular agents such as idelalisib (CAL-101 or GS-1101), ibrutinib (PCI-32765), BCL-2 inhibitors (ABT-263 (navitoclax) and ABT-199 (venetoclax)), chimeric antigen receptors (CART19 cells), novel monoclonal antibodies, and immunomodulatory drugs try to balance between survival and programmed cell death in the pathobiology of the disease. The ongoing clinical trials focusing on the combinations of kinase inhibitors with monoclonal antibodies and other pro-apoptotic agents may lead to the chemotherapy-free protocols for the indolent incurable long disease course of B-CLL. With the greater clinical experience following more widespread use of novel molecules, the optimal combination therapies in the treatment-naive and relapsed/refractory patients will be determined, resulting in more individualized therapeutic strategies for patients with CLL.

Keywords: B-cell receptor, Idelalisib, Ibrutinib, Chronic lymphocytic leukemia

ÖZET

Kronik Lenfositik Löseminin Moleküler Yönetimi: Kemoterapiden Bağımsız Bir Yaklaşıma Doğru

B hücre reseptör (BHR) sinyalleri, B hücreli malignansilerdeki tümör gelişiminde kavşak yolak görevi görürler. BHR sinyallerini ayarlayan Bruton tirozin kinaz (BTK) inhibitörleri ve fosfatidilinositol 3-kinaz-delta (PI3K) bir çok klinik çalışmada yer almış ve kronik lenfositik lösemi (KLL) gibi B hücreli lenfoproliferatif hastalıklarda yüksek yanıt oranları göstermişlerdir. KLL tedavisindeki yeni hedef proliferasyon ve apoptoz arasındaki dengedir. Yeni geliştirilen hedefe yönelik ajanlardan idelalisib (CAL-101 veya GS-1101), ibrutinib (PCI-32765), BCL-2 inhibitörleri (ABT-263 (navitoclax) ve ABT-199 (venetoclax)), kimerik antijen reseptörleri (CART19 hücreleri), yeni monoklonal antikorlar ve immünmodülatör ilaçlar, hastalığın patobiyolojisindeki programlanmış hücre ölümü ve sağkalımı arasındaki dengeyi sağlamaya çalışmaktadırlar. Kinaz inhibitörleriyle monoklonal antikor kombinasyonları ve diğer pro-apoptotik ajanlara odaklanmış halen süren kinik çalışmalar sayesinde B-KLL'nin uzun ve indolen hastalık seyrine yönelik kemoterapiden bağımsız tedavi protokolleri ortaya çıkabilir. Yeni moleküllerin yaygın kullanımı sonucu ortaya çıkacak büyük klinik tecrübe ile hiç tedavi verilmemiş ve relaps/refrakter hastalara yönelik optimal kombinasyon tedavileri belirlenebilecek, böylece KLL hastalarında daha bireyselleştirilmiş tedavi stratejileri ortaya konabilecektir.

Anahtar Kelimeler: B-hücre reseptörü, Idelalisib, Ibrutinib, Kronik lenfositik lösemi

INTRODUCTION

Chronic lymphocytic leukemia (CLL), as an indolent and incurable form of clonal leukemic disease, typically occurs in the elderly patients with co-morbidities and has a long lasting heterogenous disease course. The clinical stage of CLL disease, the fitness of the patient, the genetic risk of the leukemia, and the treatment situation (frontline versus second-line, response vs non-response to the last treatment) are the main factors in the clinical decision making in CLL. The treatment, particularly with the chemotherapeutic cytotoxic drugs having numerous adverse effects, should not be worse than the CLL disease itself. The interactions between the comorbidity and therapy of CLL suggested that the durable control of the hematologic disease is most critical to improve overall outcome of patients with increased comorbidity. Hence, the clinical disease presentations are heterogenous in CLL and the treatment decision should be based on a patient-centered individual basis rather than the disease-based fixed approach. Therefore, novel less-toxic therapeutic agents are needed, particularly for the CLL patients with comorbidities or high-risk cytogenetic abnormalities.[1] Since the significant therapy-related toxicities and the indolent/incurable nature of CLL, the treatment algorithms will continue to be revised to a more personalized approach in order to treat with improved efficacy devoid of unnecessary toxicity. Targeted molecular agents offer much promise in terms of efficacy, toxicity, and oral availability. They will change the management of patients with CLL. The main pharmacobiological basis of novel therapeutic molecules in CLL is that their mechanism of action targets a relatively specific signaling abnormality or redirects the immune system against leukemic cells. Immune reconstitution remains an enticing prospect in CLL, as malignant B cells should be particularly susceptible to a T cell-mediated attack. The pharmacological inhibitors targeting different kinases of B-cell receptor (BCR) signalling cascade, such as Bruton tyrosine kinase (BTK) and phosphatidylinositol-3-kinase (PI3K) have been developed.[1-3] Introductions of those BCR kinase inhibitors have the potential to eliminate the role of chemotherapy in the treatment of CLL.[1,2] Novel molecular agents such as BCL-2 inhibitors (ABT-263 (Navitoclax) and ABT-199 (Venetoclax), chimeric antigen receptors (CART19 cells), novel monoclonal antibodies, and immunomodulatory drugs for the pharmacobiological management of CLL are depicted in Table 1.

The aim of this review is to outline the pharmacobiology and clinical data of the novel molecular agents, particularly ibrutinib (PCI-32765) inhibiting BTK2 and idelalisib (CAL-101 or GS-1101) inhibiting PI3K3, effective in the clinical care of CLL.

CLL Management at the Molecular Level

BCR is essential for normal B-cell development and maturation. On the other hand, BCR signaling is implicated as a pivotal pathway in tumorigenesis.[4] Chronic activation of the BCR engages multiple intracellular pathways. BCR signaling can be targeted with new, small molecule inhibitors of the spleen tyrosine kinase (Syk), BTK, or phosphoinositide 3'-kinase (PI3K) isoform p110delta15 (PI3Kdelta). PI3K/AKT pathway antagonizes apoptosis, through interfering with downstream proteins. This activation of Akt leads to increased survival in a dual fashion: first, by inhibiting activation of apoptosis and also by activating NF-κB.[5,6] The cytotoxicity and mechanisms of cell death induced by the delta isoform-specific phosphatidylinositide 3-kinase (PI3K) inhibitor, idelalisib, in combination with the HDI, panobinostat (LBH589) and suberoylanilide hydroxamic acid (SAHA) have been investigated.[7] PI3Kα and PI3Kβ are ubiquitously expressed in all cells and tissues, whereas PI3Kγ and PI3Kδ are mainly enriched in leukocytes and PI3Kδ is the primary PI3K isoform in leukocytes. PI3Kδ is under the control of RTKs and antigen receptors. Class I PI3Ks produce the second messenger PIP3, which promotes cell survival, proliferation, metabolism, motility and differentiation. Aberrant PI3K activities are frequently observed in many types of cancers through different mechanisms including (but not limited to) hyperactivated RTKs, mutant Ras, functional loss of PTEN and activating mutations and/or overexpression of PI3K isoforms.[8] CLL management at the molecular level is illustrated in Figure 1.

Table 1. Novel molecular agents for the pharmacobiological management of CLL

Drug/ Pharmacological Agent	Molecular Target(s)	Current Clinical Trials
Kinase inhibitors		
Idelalisib (CAL-101, GS-1101)	PI3Kδ	Phase III
Ibrutinib (PCI-32765)	BTK	Phase III
AMG 319	PI3Kδ	Phase I
IPI-145	PI3Kγ and δ	Phase I/III
CC-292 (AVL-292)	BTK	Phase I
ONO-4059 (GS-4059)	BTK	Phase II
GS-9973	Syk	Phase II
CC115	mTOR and DNA-PK	Phase I
Dasatinib	BCR–ABL and SRC kinases	Phase II
Fostamatinib	Syk	Phase I/III
Monoclonal Antibodies		
Obinutuzumab (GA101)	CD20	Phase III
BI 836826 (moAb 37.1)	CD37	Phase I
TRU-16 (otlertuzumab)	CD37	Phase I/II
Blinatumomab (MT103/MEDI538)	CD19	Phase I
BCL-2 Antagonists		
ABT-199 (venetoclax)	BCL-2	Phase II/III
Immunomodulators		
Lenalidomide	Multiple	Phase III
CARTs		
CTL019	CD19	Phase I/II

PI3K-mediated phosphorylation activates the serine/threonine kinase AKT and mTOR. PI3Ks are lipid kinases that regulate diverse cellular processes including proliferation, adhesion, survival, and motility. Dysregulated PI3K pathway signaling occurs in one-third of human tumors.[9] Over-expression of PI3K/AKT contributes to the pathogenesis of various lymphoid malignancies, including CLL. Inhibition of PI3K results in cellular death through apoptosis. PI3K-delta subunit could exhibit significant clinical activity in CLL. Idelalisib (CAL-101, GS-1101) and IPI-145 (INK-1147) are the oral PI3K-delta inhibitors in the drug development stages.[10] Idelalisib and fostamatinib which inhibit the delta isoform of PI3 kinase (PI3Kd) and spleen tyrosine kinase (Syk) have shown significant clinical activity.[11] Idelalisib (GS-1101) is an orally bioavailable, potent, and selective inhibitor of the p110δ isoform that is currently under clinical evaluation in B-cell malignancies.[5] Inhibition of PI3K has been demonstrated to produce durable treatment responses and improved survival outcomes in clinical trials involving patients with indolent forms of NHL. PI3K inhibited by idelalisib can produce clinical responses in CLL.[1,12] Life cycles of CLL cells involve homing and egression in the patients. The migration of leukemic cells from the peripheral blood to the lymph nodes, spleen, and bone marrow, where they are become activated by micro-environmental stimuli, leads to survival and proliferation. Inhibition of PI3Kδ may interfere with this cycling at various levels, resulting in the mobilization of tissue-resident CLL cells into the blood and blocking re-entry to the stroma.[13]

CLL cells in the lymph node and bone marrow microenvironments demonstrate higher levels of BCR and NF-κB signaling.[14] Mechanisms of BCR activation may include chronic antigenic drive by
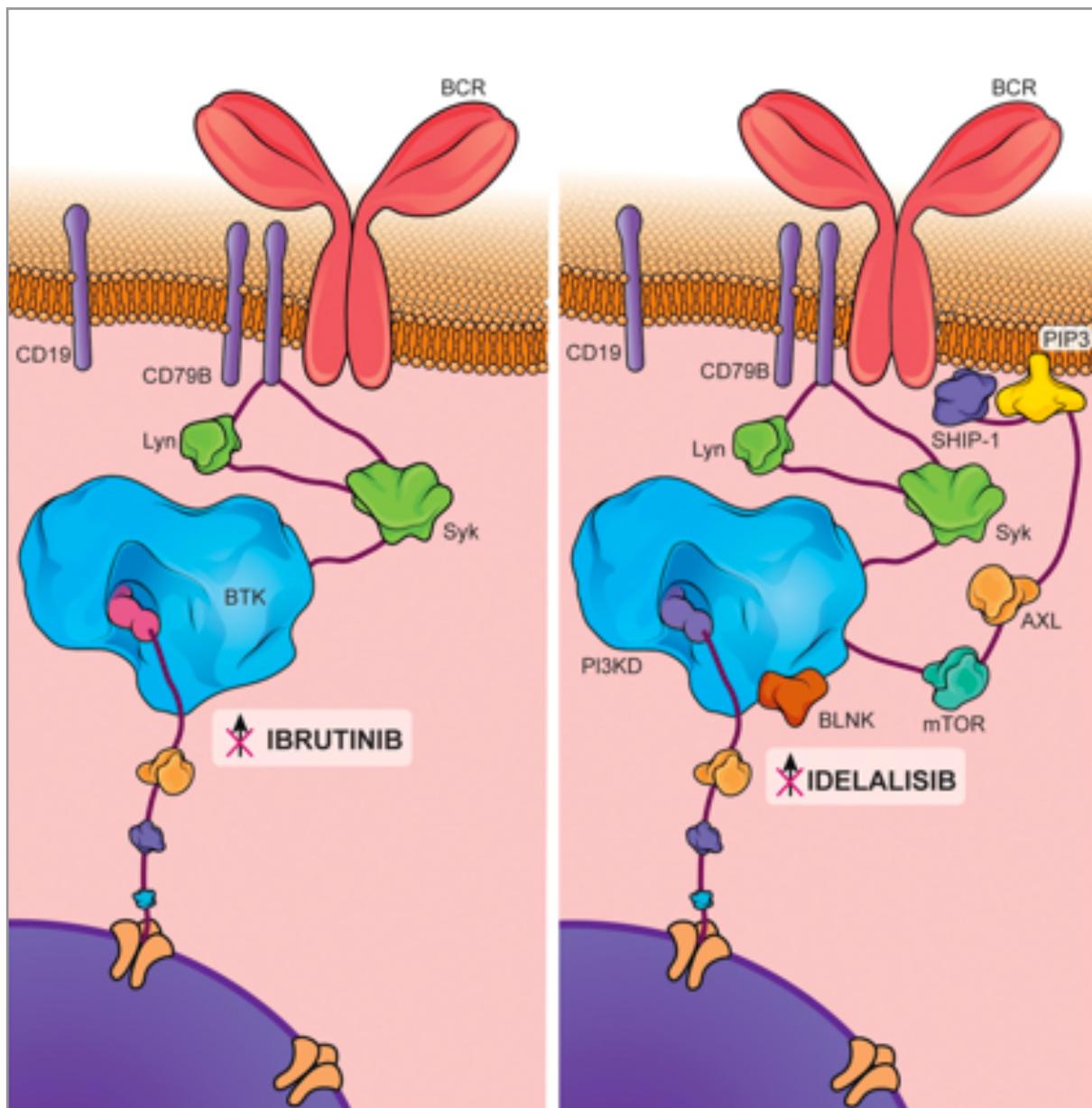
Figure 1. Chronic lymphocytic leukemia (CLL) management at the molecular level. B-cell receptor (BCR) signaling is implicated as a pivotal pathway in tumorigenesis. Chronic activation of the BCR engages multiple intracellular pathways. BCR signaling can be targeted with the drugs [Ibrutinib (against BTK) or idelalisib (against PI3KD)] to control neoplastic disease.

microbial or viral antigens, auto-stimulation of B-cells by self-antigens, and activating mutations in the intracellular components of the BCR pathway.[4] B-lymphocytes have critical functions in the immune response, including antigen presentation, antibody production, and cytokine release. BCR, which is activated by binding to antigen, can induce receptor aggregation together with the activation of multiple tyrosine kinases and downstream signaling pathways.[4]

BTK is a Tec family cytoplasmic tyrosine kinase that is a key component of BCR signaling pathway and is critical for normal B cell development, differentiation, proliferation and survival. BTK is a 659-amino-acid protein that contains five signaling domains and has diverse partner molecules.[15] BTK transmits, diversifies, and amplifies signals from a wide variety of surface molecules that cells use to communicate with their microenvironment. BTK is a central signaling node mediating the nourish-

ing and protective effects of the tumor microenvironment.[16] BTK is also essential for the homing of MCL cells into lymphoid tissues, and its inhibition results in an egress of malignant cells into peripheral blood.[17] The absence of BTK predominantly affects B cell function. In the absence of BTK, BCR signaling is insufficient to induce late transitional B cells to differentiate into mature peripheral B cells. BCR signaling pathway genes are constitutively increased in B cell tumors, manageable via the therapeutics targeting BTK. BTK inhibition had decreased DNA synthesis and prosurvival signal from stromal cells and cytokines.[15,18]

Pathobiological expression of the B-cell receptor (BCR) signaling can cause disease progression in the malignant B-cell neoplastic diseases.[19] Bruton's tyrosine kinase (BTK) has a pivotal role in the BCR signaling. Normal B lymphocytes receive signals from BCR that are triggered by binding of the BCR to an external antigen. Tonic signaling through the BCR provides growth and signals to CLL cells, and plays an important role in the pathogenesis and progression of the disease.[20] BTK is a cytoplasmic tyrosine kinase transmitting neoplastic signals from the BCR and tissue homing receptors.[21] BTK inhibitor ibrutinib is a novel targeted-therapeutic agent which serves as a covalent irreversible inhibitor of BTK.[22] Bruton tyrosine kinase, have generated the most promising early results in clinical trials including predominately refractory CLL where durable disease control has been observed.[23-29] BTK is a critical kinase for CLL development and expansion and thus an important target of ibrutinib.[30] Ibrutinib causes an early redistribution of tissue-resident CLL cells into the blood, with rapid resolution of enlarged lymph nodes, along with a surge in lymphocytosis. After weeks to months of continuous ibrutinib therapy, the growth- and survival-inhibitory activities of ibrutinib result in the normalization of lymphocyte counts and remissions in a majority of patients with CLL.[31]

Ibrutinib can induce the redistribution of malignant B cells from tissue sites into the peripheral blood together with the rapid resolution of enlarged neoplastic lymph nodes.[21] Ibrutinib significantly alters the composition of the tumor microenvironment in CLL, affecting soluble as well as cellular molecular

elements.[32] Ibrutinib does not cause myelosuppression.[22] With continuous ibrutinib therapy, growth- and survival-inhibitory activities of ibrutinib could result in the normalization of lymphocyte counts and remissions in the patients with B-cell neoplastic diseases. Ibrutinib is the first BTK inhibitor that is being used and approved in the clinical practice with the most mature clinical data.[33] The drug was designed as a selective and irreversible inhibitor of the BTK protein, and it inhibits signal transduction from the BCR and blocks activation of B cells.[18]

Ibrutinib can effectively inhibit neoplastic pathways that promote tumor cell activation and proliferation.[2,34,35] Herman and coworkers[16] evaluated the in vivo effects of ibrutinib, the BTK inhibitor on tumor cell activation and proliferation in the peripheral blood, lymph nodes, and bone marrow of the patients with CLL.[16] They detected a rapid and sustained down-regulation of BCR and NF-kappaB signaling in CLL cells from both the peripheral blood and tissue compartments during ibrutinib treatment. In their study, ibrutinib significantly decreased tumor proliferation and expression of surface activation markers CD69 and CD86 independent of the well-known CLL prognostic factors such as IGHV mutational status,

Anti-Neoplastic Activities of Novel Molecular Agents in CLL

Multiple pathobiological factors can contribute to BCR dysregulation in CLL. BCR activation can be influenced by the immunoglobulin structure, the expression and mutations of adaptor molecules, the activity of kinases or phosphatases and the levels of microRNAs.[36] The crosstalk of BCR with other signalling pathways (NF-kappaB, adhesion, chemokine signalling) are also evident.[36] PI3K inhibitors regulate pathway activities in both cancer and stromal cell populations.[37] Key pathways orchestrated by PI3Kd and turned on in B-cell malignancies upon BCR activation include membrane trafficking, AKT/mTOR, MAPK, and NF-kB.[12,23] AKT is the best-characterized downstream effector of PI3Kd and is the central modulator of PI3K-regulated oncogenic signaling. Many oncogenic effectors downstream of AKT play critical roles in regulating cell cycle and cell survival, DNA repair (MDM2 and p53), chemoresistance (NF-kB), and

energy metabolism (mTOR); many of these targets are inhibited by pan-PI3K or PI3Kd-specific inhibitors.[38] Ibrutinib inhibits activation and proliferation of CLL cells in vivo. On-target effects of BTK inhibition in tissue-resident CLL cells were shown. Blocking cell proliferation via inhibition of BTK-mediated signaling may contribute to clinical responses in ibrutinib-treated patients.[39] Binding site between ibrutinib and BTK is well described.

The chemokines in tumor cell-microenvironment interactions represent a target for treatment of CLL.[40] Chemokine receptors expressed on CLL cells regulate the migration of the leukemia cells within the bone marrow, lymphoid organs in collaboration with chemokines. Furthermore, chemokines produced in distinct tissue microenvironments sustain migration of mature lymphocytes in lymphoglandula. Chemokines form a pro-survival circuitry by regulating leukocyte trafficking, maintaining extended lymphocyte survival.[40] A potentially dangerous subpopulation of CLL cells equipped to migrate to tissue and receive a proliferative stimulus.[41] In addition, PI3Kd regulates B-cell responses to CD40-ligand, B-cell activating factor (BAFF), IL4, and to the homing chemokines CXCL12/13.[2,3,9] The expression of chemokines such as C-C motif ligand 3 and 4 (CCL3/4), as well as stroma-/Tcell–produced factors, including CD40L, TNFa, IL6, and IL10, was also reduced.[3,35] Idelalisib may thus simultaneously target the malignant B cells by inhibiting their response to stromal factors and the tumor niche by limiting its ability to support the tumor cell growth.[42] Ibrutinib inhibits the migration of CLL cells in chemokine gradients. Chemokine signaling is blocked by ibrutinib so that the neoplastic migration of the B-cells is impaired.[43]

The reduction of tissue disease burden by ibrutinib is due more to CLL cell death and less to egress from nodal compartments.[44] Moreover, rapid and sustained reduction of the cellular activation and tumor proliferation has been shown to be achieved by ibrutinib in all of the anatomic compartments related to the neoplastic development of CLL disease course.[38] Ibrutinib may alter the composition of the bone marrow microenvironment lead to a transient increase in circulating CLL cells consistent with the efflux of activated cells from the

tissue compartments leading to the reduction in lymphadenopathy.[28] Ibrutinib-induced early-onset lymphocytosis[45] develops within hours due to the release of previously activated resident cells from the tissue microenvironments. The rapid onset of the lymphocytosis and the dramatic defect in the adhesion process suggested that ibrutinib directly interferes with an intracellular signaling network required for cell adhesion.[46] In vitro idelalisib reduced CLL migration beneath a layer of bone marrow–derived stromal cells, inhibited CLL adhesion to stromal and endothelial cells, and decreased chemotaxis toward CXCL12 and CXCL13. These observations are consistent with the rapid decrease in lymph node size and increase in lymphocytosis in idelalisib-treated patients and are a possible indication of tumor cells being separated and migrating away from the tumor niche.[42,47] No cases of ibrutinib-induced leukostasis were reported in subjects with CLL/SLL receiving ibrutinib, although subjects with a high number of circulating malignant cells (> 400.000 k/uL) should be closely monitored. In subjects with CLL receiving ibrutinib in combination[48] with chemoimmunotherapy or immunotherapy, lymphocytosis appeared to occur in lower incidence and at lesser magnitude. The lymphocyte counts of the majority of CLL patients return to baseline lymphocyte values by the end of cycle 5.[49,50] Idelalisib, like other novel agents targeting the B-cell–receptor signaling pathway, has been shown to cause lymphocytosis when it is administered as a single agent. The addition of rituximab to idelalisib blunted and shortened the duration of the lymphocytosis, which confirmed the findings of a previous phase 1 study. In contrast, there was a sustained increase in the absolute lymphocyte count in the placebo group starting at week 24, which coincided with the completion of rituximab therapy. As per the modified IWCLL guidelines, this rise in the lymphocyte count was not considered to be disease progression.[47,51]

Clinical Trials of Molecular Agents in CLL

In the phase 1 trial[47], idelalisib, a selective inhibitor of the lipid kinase PI3Kdelta, has been evaluated in 54 patients with relapsed/refractory CLL with adverse characteristics including bulky lymphadenopathy (80%), extensive prior therapy

(median 5 [range 2-14] prior regimens), treatment-refractory disease (70%), unmutated IGHV (91%), and del17p and/or TP53 mutations (24%). In this study[47], the patients with CLL in this trial were treated at 6 dose levels of oral idelalisib (range 50-350 mg once or twice daily) and remained on continuous therapy until progression. Idelalisib treatment resulted in nodal responses in 81% of patients in this study. The overall response rate was 72%, with 39% of patients had the partial response. The median progression-free survival those CLL patients was 15.8 months.[47]

O'Brien et al present the first clinical trial of idelalisib with rituximab for the initial therapy of CLL in patients with a median age of 71 years, 42% of whom had advanced-stage disease. The overall response rate in this phase II study is 97%, with 19% being complete responders, none of whom have progressed to date. The progression-free survival (PFS) is an impressive 83% at 36 months, with only 4 events of disease progression, despite only 23 of 64 patients currently continuing on idelalisib. Among the highest-risk TP53-mutated patients (n= 9), the overall response rate is 100% and none have progressed, consistent with the known excellent activity of idelalisib in relapsed patients in this high risk group. Although this was a phase 2 study, these results compare very favorably with the current standard of care for this patient population—obinutuzumab chlorambucil—which has a median PFS of 29.2 months in a phase 3 study[51], and are similar to the smaller phase 1b/2 study of ibrutinib, which showed a PFS of 96% at 30 months,4 with only 2 TP53-mutated patients. These results certainly justify registration trials of idelalisib in this upfront setting.[50]

The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy in a multicenter, randomized, double-blind, placebo-controlled, phase III 116 study.[52] Eligible patients needed to have disease progression within 24 months of their last treatment, previously received anti-CD20 therapy or ≥ 2 prior cytotoxic therapies and had current contraindications to cytotoxic therapy. The authors randomly assigned

220 CLL patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses to receive rituximab 375 mg/m² intravenously for the first cycle and at 500 mg/m² intravenously on subsequent cycles (cycles were every 2 weeks for 5 doses, then monthly for 3 doses) and either idelalisib at a dose of 150 mg or placebo twice daily. The primary end point in their study was progression-free survival. There were no statistically significant differences in baseline characteristics between the groups, with 78% of all patients being ≥ 65 years old, > 80% having unmutated IGHV, > 40% having a 17p deletion, and 85% having a Cumulative Illness Rating Scale (CIRS) score of more than 6. Based on the results of this study, The 24-week PFS was 93% and 46% for the idelalisib and placebo groups, respectively, which resulted in the trial being stopped early due to treatment efficacy. The median PFS was 5.5 months in the placebo group and was not reached in the idelalisib group (p< 0.001). The median duration of idelalisib and placebo treatment was 3.8 and 2.9 months, respectively, though 81% of idelalisib patients were continuing treatment at study termination compared to 52% of patients receiving placebo. Disease progression occurred in 12 patients in the idelalisib group and in 53 patients in the placebo group. The patients receiving idelalisib versus those receiving placebo had improved rates of overall response (81% vs. 13%; p< 0.001). On the basis of a review of imaging results by the independent review committee, the proportion of patients with a reduction of 50% or more in lymphadenopathy was significantly higher in the idelalisib group than in the placebo group (93% vs. 4%), for an odds ratio of 264 (p< 0.001). The most impressive finding was that idelalisib and rituximab treatment had similar efficacy regardless of the presence of 17p deletion or IGHV mutational status. A secondary endpoint overall survival at 12 months was 92% vs. 80%; p= 0.02 (odds ratio, 29.92; p< 0.001). All responses were partial responses. Sixteen patients died while participating in the study: 4 patients (4%) in the idelalisib group and 12 patients (11%) in the placebo group. More than 90% of patients experienced at least one adverse event. The most common adverse events in the idelalisib group were pyrexia, fatigue, nausea, chills, and diarrhea. Grade 3 or 4 neutropenia, thrombocytope-

Table 2. Selected critical clinical trials of the novel molecular agents in CLL

Drug	Other agents in com- bination	Clinical Trial	Phase	Disease Status	Response	Reference
Ibrutinib		Safety of PCI-32765 in chronic lymphocytic leukemia	Phase Ib/II	> 65 y tx-naive R/R or high risk any age	ORR: 71%	Byrd JC, et al. N Engl J Med 369:32-42, 2013
Ibrutinib	BR	Safety and tolerability study of PCI-32765 combined with bendamustine/rituximab (BR) in chronic lymphocytic leukemia (CLL)	Phase Ib	R/R	ORR: 93% CR: 13% PFS: 90% at 12 months	Brown JR, et al Blood 2013; 120 (Suppl1): 525A
Ibrutinib	Rituximab	Ibrutinib (PCI-32765) in combination with rituximab is well tolerated and induces a high rate of durable remission in patients with high-risk chronic lymphocytic leukemia	Phase II	High-risk	ORR: 95% CR: 8% PFS: 80% at 14 months	Burger JA, et al Blood 2013; 120 (Suppl. 1): 675A
Ibrutinib versus ofatumumab (Resonate)		Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia	Phase III	R/R	ORR: 42,6% (Ibrutinib) vs 4,1% (ofatumumab) p< 0.001	Byrd JC, et al N Engl J Med 371:213-23, 2014
Idelalisib	Rituximab	A randomized, double-blind and placebo-controlled study of idelalisib in combination with rituximab for previously treated chronic lymphocytic leukemia (CLL)	Phase III	R/R	ORR: 81% (Idelalisib; R) vs 13% (placebo, R) Median PFS: 5,5 months in placebo, NR in idelalisib, R. Median PFS: 19,4 months	Furman RR, et al N Engl J Med 370: 997-1007 2014 Sharman, ASH, 2014, Abstract 330
Idelalisib		Idelalisib, an inhibitor of phospha tidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia	Phase I	R/R	ORR: 72% Median PFS 15,8 months	Brown JR, et al Blood 123: 3390 -3397, 2014
Idelalisib		Randomized, placebo-controlled study of Idelalisib plus bendamustine and rituximab (BR) is superior to BR alone in patients with relapsed/refractory chronic lymphocytic leukemia	Phase III	R/R	ORR: 68% Idelalisib+BR vs 45% BR CR: 5% Idelalisib+BR vs 0% BR Median PFS 23,1 months	December 03, 2015; Blood: 126 (23)
ABT-199	Rituximab	A phase 1b study evaluating the safety and tolerability of ABT-199 in combination with rituximab in subjects with relapsed chronic lymphocytic leukemia and small lymphocytic lymphoma	Phase Ib	R/R	39% CR/CRi 5/7 CR patient MRD negative	Ma S, et al. J Clin Oncol 5s, 2014;32 7013A

R/R: Relapsed Refractory; BR: Bendamustine, Rituximab; High-risk: del17p or TP53 mutation /treated or untreated), PRS <36 month after frontline immunotherapy or relapsed CLL with del11q

nia, anemia, elevations in aminotransferases, and diarrhea occurred in 34%, 10%, 5%, 5%, and 4% of patients, respectively.[52]

Andrew D Zelenetz et al presented the results of a randomized, placebo-controlled, phase III 115 study that evaluated the efficacy of IDELA added to BR, a common regimen for relapsed/refractory (R/R) CLL. 416 patients (pts) with R/R CLL were enrolled. Patients were randomized to BR for 6 cycles Q 28 days (B= 70 mg/m^2 D1, D2 of each cycle; R= 375 mg/m^2 C1 and 500 mg/m^2 C2-6) and IDELA 150 mg BID or placebo (administered continuously). A pre-specified interim analysis (IA) was performed with a median follow up 12 months demonstrating that PFS, the primary endpoint, and OS, a secondary endpoint, were superior in the investigational vs control arm with a safety profile consistent with prior reported studies. Rai stage III/IV 46%; median time since completion of last prior therapy 16 months; patients with del(17p)/p53mut 32.9%, patients with unmutated IGHV 83.2%, patients with refractory disease 29.8%, median number of prior therapies: 2 (range: 1-13). Median PFS of IDELA + BR vs BR + placebo: 23 mo vs 11 mo (HR= 0.33; p< 0.0001), median OS of IDELA + BR vs BR + placebo not reached for either arm (HR= 0.55; p= 0.008). Addition of IDELA to BR was also beneficial in pts withoutdel(17p)/TP-53mut. The most common all-grade AEs with IDELA + BR were neutropenia and pyrexia (63.3% vs 41.5%), and with BR + placebo were neutropenia and nausea (53.6% vs 34.4%). The most common grade ≥ 3 AE was neutropenia (59.9%). Grade≥ 3 diarrhea with IDELA + BR was 7.2% and BR + placebo was 1.9%.[53]

Idelalisib has been approved by FDA in combination with rituximab for relapsed CLL in USA. In Europe, EMA also approved idelalisib-rituximab combination in relapsed/refractory patients as well as the front-line CLL treatment in the presence of 17 pDel or TP53 mutation in patients unsuitable for the chemoimmunotherapy. EMA/Europe approved ibrutinib for chronic lymphocytic leukaemia patients who have received at least one previous treatment, and in patients who have genetic mutations in their cancer cells called 17p deletion or TP53 mutation that make them unsuitable for treatment with a combination of chemotherapy

medicines and immunotherapy, for mantle cell lymphoma patients whose disease does not respond to or has come back after previous treatment.[53]

Future Perspectives

The pharmacological down-regulation of BCR activity is an attractive novel strategy for treating patients with B-cell malignancies particularly CLL. In addition to idelalisib and ibrutinib, BCL-2 antagonists such as navitoclax is under progress for the management of CLL. Navitoclax is a potent inhibitor of pro-apoptotic proteins. However, its efficiency is limited by the adverse effect of thrombocytopenia. Therefore, the drug has been re-engineered into ABT-199 (venetoclax) with less profound thrombocytopenia due to selective inhibition of BCL-2 dependent tumor growth. Those molecules are under progress in distinct clinical drug development stages (Table 1 and Table 2).

The modulation of neoplastic signaling as well as the molecular interactions between CLL cells and stromal microenvironment will be translated into clinical trials that would be very helpful for the better management of the patients. The integration of the novel targeted agents for CLL therapy into sequential treatment approaches is also vital. Selected critical clinical trials of the novel molecular agents in CLL are depicted in Table 2. With the greater clinical experience following more widespread use of novel molecules, the optimal combination therapies in the treatment-naive and relapsed/refractory patients will be determined, resulting in more individualized therapeutic strategies for patients with CLL.

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