New Treatment Perspectives in CLL: Using Disease and Patient Characteristics to Optimize Outcomes

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Abstract

Therapies for chronic lymphocytic leukemia (CLL) have evolved over the last two decades and newer treatment regimens have significantly improved patient survival. Fludarabine, cyclophosphamide, and rituximab (FCR) was the first therapy to demonstrate a survival advantage for young and fit patients with CLL, making it the gold standard treatment for these patients. However, as the CLL population is diverse in terms of patient age, fitness level, and disease characteristics, patients with CLL vary in their ability to tolerate and respond to FCR; thus highlighting the need for individualized therapy. Recently, important advances have been made in understanding CLL pathogenesis, inspiring the generation of new, targeted agents, such as ibrutinib and idelalisib, which may address the limitations of FCR. These new agents are intelligently designed to target B-cell receptor (BCR) signalling and the CLL microenvironment, resulting in alternate mechanisms of cell death that are specific to CLL cells. This review will highlight the factors currently influencing treatment decisions, the advances made in understanding CLL biology, and the novel BCR pathway inhibitors that may impact treatment decisions and patient outcomes in the future.

1. Background

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, accounting for approximately 11% of all hematological cancers in adults.[1] CLL is predominantly a disease of the elderly, with the median age being 72 years at diagnosis and approximately 75% of patients being 65 years or older.[1] In 2010, the overall age-standardized incidence rate for CLL in Canada was 4.8/100,000 people; 6.6/100,000 people for males and 3.3/100,000 people for females.[2]

Although CLL remains an incurable disease, therapies to treat CLL have evolved over the last 50 years which have significantly improved patient outcomes. Introduction of the monoclonal antibody rituximab to treatment regimens has largely contributed to these improved outcomes. Rituximab is a targeted therapy against CD20, which is expressed on the surface of CLL cells. It induces its cytotoxic effects through complement-mediated lysis, antibody-dependent cellular cytotoxicity, and direct induction of apoptosis.[3] Rituximab monotherapy demonstrates only modest response rates in patients with CLL; however, when combined with fludarabine and cyclophosphamide (FC), this regimen can achieve overall response rates (ORRs) and complete response (CR) rates of 95% and 70%, respectively.[3] In addition, rituximab plus FC (FCR) demonstrated improved overall survival (OS) compared with FC alone in a randomized, phase III trial of treatment-naïve patients with CLL.[4] This was the first ever demonstration of an OS advantage in a phase III trial in CLL and led to the approval of this regimen by the Food and Drug Administration

(FDA) in 2010. Currently, FCR is considered the gold standard treatment for younger, fit CLL patients. However, despite the promising results achieved with this chemoimmunotherapy, FCR has limitations that prevent it from being an appropriate therapy for most patients with CLL. Firstly, FCR is a therapy associated with significant toxicities. In the CLL8 and REACH trials, which investigated FC versus FCR in treatment-naïve and relapsed patients with CLL, grade 3/4 toxicities were reported in 76% and 80% of patients treated with FCR, respectively.[4,5] This level of toxicity limits the use of FCR in elderly, unfit patients with multiple comorbidities who are unable to tolerate such intensive therapy. Secondly, in the CLL8 study, it was observed that approximately one-third of patients had significant treatment resistance to FCR (progression-free survival [PFS] <24 months) that was associated with reduced OS.[6] Lastly, although the REACH trial found FCR to be efficacious in the relapsed setting, most of these patients were not previously exposed to fludarabine-based treatments.[5] It is now accepted that in patients who relapse earlier than 24–36 months after FCR therapy, retreatment with FCR is not an effective therapy and new treatment options are needed for these patients in the relapsed setting.[7,8]

As patients differ in their response and ability to tolerate therapy, it is apparent that CLL therapy needs to be individualized for each patient. This emphasizes the need to identify patient and disease characteristics that are indicators for selection of specific therapies, and also the need to develop new therapeutic agents that will be effective in the highest-risk patient subgroups. Recently, significant advances have been made in understanding the biology of CLL, inspiring the generation of new targeted agents that may address the limitations seen with FCR. In contrast to chemotherapies, these new agents are intelligently designed to target dysregulated pathways, resulting in alternate mechanisms of cell death that are specific to CLL cells. Thus, by understanding the biology of CLL, we are moving towards individualizing treatments for CLL patients.

Although many novel agents are currently being investigated in CLL, this review will focus on the B-cell receptor (BCR) signalling inhibitors, idelalisib and ibrutinib, which have been approved by Health Canada for the treatment of CLL. The purpose of this paper is to describe the current patient and disease characteristics that may influence treatment decisions, highlight the advances made in understanding CLL biology that led to the development of BCR signalling inhibitors, and to discuss the potential impact of these novel therapies on treatment decisions and patient outcomes in the future.

2. Factors influencing treatment decisions

2.1. Patient characteristics

As current CLL regimens vary in level of toxicity, one of the most influential factors when choosing a therapeutic regimen for an individual patient is his or her medical fitness. When evaluating fitness, a combination of factors including organ function, performance status, age, and comorbidities must be considered. Fitness assessment tools such as the Cumulative Illness Rating Scale (CIRS) for measuring comorbidities[9] and the Eastern Cooperative Oncology Group (ECOG) system for measuring performance status[10] are often used in clinical trials. However, in clinical practice, Canadian physicians routinely rely on personal experience and patient observation to assess fitness and make treatment decisions, as not all comorbidities are equal when it comes to predicting drug tolerability.

The German CLL Study Group (GCLLSG) has used CIRS to evaluate patient fitness in clinical trials.[11] Using tools such as the CIRS score, the GCLLSG separates patients into the following three fitness categories: 'go-go', 'slow-go', and 'no-go'.[11] This classification of patient fitness is a useful aid for defining treatment goals and making treatment decisions. The 'go-go' group of patients are typically young and fit with a long life expectancy; therefore, deep remission would be the primary goal of therapy and treatment efficacy would be the priority when choosing a treatment regimen. In contrast, the 'no-go' patients are typically frail patients with multiple or severe comorbidities and a short life expectancy. For these patients, palliation is a more appropriate goal; therefore, tolerability of therapy and maintenance of quality of life would be the priority when selecting therapy for these patients. The 'slow-go' patients fall in the middle of this spectrum and are typically less fit, with some comorbidities and an unknown life expectancy; therefore, achieving durable remission with a tolerable regimen is the goal for these patients.

For the majority of patients who fall into the 'slow-go' category, a balance between efficacy and toxicity is required when choosing therapy for these patients. The relationship between efficacy and safety of CLL therapies has been described by Shanafelt et al., and is a useful perspective to consider when choosing an appropriate therapy.[12] Generally, a strong correlation has existed between efficacy and toxicity, where historically the most effective treatments have been associated with the highest toxicities.[12] As most patients with CLL are older, have at least one comorbidity, and are unable to tolerate highly intensive therapy such as FCR, less effective therapies with fewer toxicities have been preferable.[11]

The patient's preference is another important consideration when making treatment decisions. A number of factors may affect a patient's expectations of therapy. Some patients are much more willing to accept the risks of severe toxicity in the hopes of a longer remission, while other patients prefer a less toxic regimen and are accepting of an earlier expected relapse. The need for a doctor-patient partnership when making treatment decisions is important for a disease such as CLL where there are multiple treatment options, each with different risks and benefits. As patients have to undergo treatment and accept toxicities, it is important that patient preferences are communicated and respected.

2.2. Disease characteristics

CLL is a heterogeneous disease with diverse genetic and molecular characteristics, which translates into a wide range of clinical outcomes among patients.[13] Several recurring genetic abnormalities can be seen in CLL, with the most common chromosomal abnormalities including deletions in 13q, deletions in 11q, trisomy 12, deletions in 17p [del(17p)], and deletions in 6q.[14] However, the only genetic marker that is currently used to guide treatment selection is the presence of del(17p).[15]

Patients with del(17p) have the poorest prognosis among genetic subgroups identified thus far, with very low survival rates.[14,16,17] These patients also respond poorly to fludarabine-based treatments. In the CLL8 trial, ORR in patients with del(17p) treated with FC or FCR was 34% and 68%, respectively, which was markedly lower than the ORR in the total population (80% and 90%, respectively).[4] Moreover, a high proportion of refractory patients were positive for del(17p) (34.4%), and the PFS at 3 years in patients with del(17p) was very low (0% and 18% in the FC and FCR arms, respectively).[4,6] Although not directly compared, alemtuzumab in combination with steroids appears to produce better response rates than FCR for patients with del(17p), however, median PFS was still quite short, particularly in relapsed or refractory patients.[18] Because of its poor prognosis, del(17p) has been an indication for consideration of allogeneic stem cell transplantation.[19] However, a recent analysis of patients with advanced CLL who received an allograft found that del(17p) may still be an independent predictor of poor PFS and OS following transplantation.[20] This highlights the need for more effective therapies to treat CLL patients with del(17p).

The deletion of 17p results in the loss of the TP53 locus which encodes the tumour suppressor p53, a protein that plays a critical role after DNA damage by inducing cell cycle arrest and apoptosis.[13] Fludarabine and the alkylating agents function via a p53-dependent mechanism, thus explaining the poor responses of patients with del(17p) to FCR and other chemoimmunotherapies.[4,13,21] TP53 mutations, even in the absence of del(17p), have also been observed in a number of studies. In the CLL8 trial, the presence of TP53 mutations was associated with a lower ORR compared with patients with wild-type TP53 (62.1% vs. 95.3%, respectively), as well as a shorter median PFS (12.4 months vs. 45 months) and median OS (39.3 months vs. not reached).[22]

As the presence of del(17p) and TP53 mutations are associated with a poor response to conventional chemotherapy-based treatment, analysis for these genetic lesions is recommended prior to treatment initiation to identify patients who require alternative therapies.[23] The incidence of del(17p) and TP53 mutations in patients with CLL at diagnosis is approximately 4–5% and 5–10%, respectively.[23] This incidence significantly increases at relapse through a process of acquisition of genetic aberrations called clonal evolution.[16,24] Indeed, in relapsed and fludarabine-refractory patients with CLL, the incidence of del(17p) and TP53 mutations has been reported to be up to 30% and 40%, respectively.[23] This supports the recommendation of a thorough search for TP53 mutations/deletions to be performed before each line of therapy.

3. Understanding the molecular mechanisms driving CLL

3.1. CLL microenvironment

A deeper understanding of the mechanisms of CLL pathogenesis is imperative for the development of novel therapies. At the cellular level, CLL is characterized by the accumulation of mature, non-functional, CD5+, CD19+, CD20+, and CD23+ B-lymphocytes in the blood, bone marrow, and lymphoid tissue.[25] This accumulation of CLL cells was once thought to be strictly a result of impaired apoptosis; however, it is now recognized that an increase in cell proliferation also contributes to the expansion of the CLL clone. Proliferation of CLL cells occurs in distinct anatomical tissue sites called pseudofollicles located in the bone marrow and lymphoid tissues.[26] Within these pseudofollicles, CLL cells interact with accessory cells, including T cells, mesenchymal stromal cells, and monocyte-derived nurse-like cells (NLCs), which, along with matrix factors, make up the CLL microenvironment.[26]

The homing and retention of CLL cells to this microenvironment play a critical role in the maintenance of the CLL clone, presenting an attractive target for therapy. The expression and function of chemokine receptors and integrins on CLL cells is essential for this homing to occur.[27] The chemokine receptor CXCR4, which is expressed at high levels on CLL cells in the blood, mediates CLL cell chemotaxis and migration beneath bone marrow stromal cells in response to CXCL12 gradients secreted by stromal cells and NLCs.[28,29] Similarly, very late antigen-4 (VLA-4) integrin expression on CLL cells, which plays a critical role in lymphocyte trafficking, adhesion, and survival in normal B cells, increases the ability of CLL cells to access protective niches by interacting with vascular cell adhesion molecule-1 (VCAM-1) and fibronectin on stromal cells.[30,31]

The protective effect of the CLL microenvironment is a product of the complex interactions between CLL cells, accessory cells, and matrix factors that induce survival and proliferative pathways. CLL cell survival can be induced by engagement with the ligands B-cell activating factor of the tumour necrosis factor family (BAFF), CD40L, and a proliferation-inducing ligand (APRIL), which are expressed on the surface of accessory cells.[32,33] In addition, a recent study that analyzed gene expression in blood, bone marrow, and lymphoid samples from 24 patients with CLL showed that the gene sets associated with the BCR pathway and nuclear factor κB (NF-κB) pathway had the most striking differential expression between tissues,

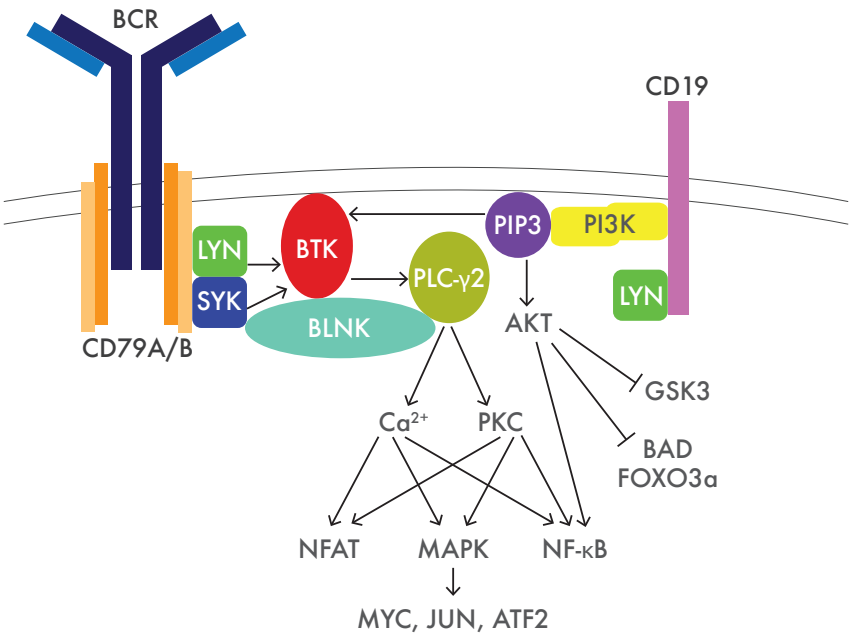
with significant up-regulation in the lymph nodes.[34] This indicates the prominent role of BCR signalling within the CLL microenvironment. The details of this signalling pathway in normal and malignant B cells are described in the following section.

3.2. BCR signalling

Dysregulated BCR signalling has emerged as a key mechanism in CLL pathogenesis. Although the precise mechanism of BCR stimulation is unknown, the BCR has been reported to be activated by antigen binding and by antigen-independent autonomous signalling mechanisms.[35] The BCR is composed of a ligand binding moiety, consisting of an antigen-specific membrane immunoglobulin, and a signal transduction moiety, consisting of two membrane-spanning proteins – Immunoglobulin-associated alpha (CD79A) and Immunoglobulin-associated beta (CD79B).[26] Upon BCR activation, the SRC-family tyrosine kinase LYN is recruited to the receptor where it phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAMs) on the intracellular portion of CD79A and CD79B.[36] The spleen tyrosine kinase (SYK) is subsequently recruited to phosphorylated ITAMs where it too becomes phosphorylated and activated by LYN.[36] SYK and LYN then play an essential role in BCR signalling by initiating several pathways (Figure 1).

SYK phosphorylates B-cell linker protein (BLNK), which acts as a scaffold to bind Bruton's tyrosine kinase (BTK) and phospholipase C-γ2 (PLC-γ2).[37] PLC-γ2 is then activated by phosphorylation from both SYK and BTK.[37] Activation of PLC-γ2 initiates the second messengers diacylglycerol and inositol triphosphate, which subsequently activate protein kinase C (PKC) and calcium influx, respectively. Both PKC and intracellular calcium can activate the transcription factors NF-κB and nuclear factor of activated T cells (NFAT).[36,37] PKC can also activate mitogen-activated protein kinase (MAPK) pathways, leading to activation of transcription factors such as MYC, JUN, and activating transcription factor-2 (ATF2), which are important for promoting cell survival and proliferation.[36,37] In addition, LYN phosphorylates CD19, leading to the recruitment and activation of phosphoinositide 3-kinase (PI3K). Recruitment of PI3K to the plasma membrane leads to the production of phosphatidylinositol 3,4,5-triphosphate (PIP3), which is required for optimal activation of BTK, as well as the activation of AKT.[36] AKT promotes survival by activating transcription factors such as NF-κB, phosphorylating and disrupting the proapoptotic functions of BCL2-associated agonist of cell death (BAD) and forkhead box O3 (FOXO3a), and by enhancing nuclear accumulation of NFAT through the phosphorylation and inhibition of glycogen synthase kinase 3 (GSK3).[37]

Figure 1. B-cell receptor signalling



AKT = v-akt murine thymoma viral oncogene homolog protein; ATF2 = activating transcription factor 2; BAD = BCL2-associated agonist of cell death; BCR = B-cell receptor; BLNK = B-cell linker protein; BTK = Bruton's tyrosine kinase; Ca2+ = calcium ion; CD = cluster of differentiation; FOXO3a = forkhead box O3a; GSK3 = glycogen synthase kinase 3; JUN = jun proto-oncogene protein; LYN = LYN proto-oncogene, Src family tyrosine kinase protein; MAPK = mitogen-activated protein kinase; MYC = v-myc myelocytomatosis viral oncogene homolog protein; NFAT = nuclear factor of activated T-cells; NF-κB = nuclear factor of kappa light polypeptide gene enhancer in B-cells; PIP3 = phosphatidylinositol 3,4,5-triphosphate; PI3K = phosphoinositide 3-kinase; PKC = protein kinase C; PLC-κ2 = phospholipase C-κ2; SYK = spleen tyrosine kinase

In tumour samples from CLL patients, both the levels and activation of LYN and SYK have been shown to be up-regulated.[38,39] Moreover, downstream of LYN and SYK, the BTK and PI3K pathways have also been reported to be amplified in CLL.[37] In addition to activating cell survival and proliferation, BCR stimulation in CLL cells can also induce the secretion of chemokines, including CCL22, CCL3, and CCL4, which can attract accessory cells, such as T cells.[40,41] This indicates that CLL cells may also play an active role in creating and maintaining their own microenvironment.[42]

4. Novel therapeutic agents targeting BCR signalling

Given the substantial role of BCR signalling in CLL pathogenesis, new therapies have been developed to target this pathway. Currently, ibrutinib (IMBRUVICA®, Janssen Inc.) and idelalisib (Zydelig®, Gilead Sciences Canada, Inc.), which inhibit BTK and PI3K-δ respectively, have demonstrated efficacy in phase III clinical trials in CLL. Although several other agents that target the BCR pathway are being investigated, the following section will focus on ibrutinib and idelalisib, which have been approved by Health Canada for use in patients with CLL.

4.1. Ibrutinib

4.1.1. Mechanism of action

Ibrutinib is the first-in-class, irreversible inhibitor of BTK that covalently binds to Cysteine-481 in the ATP binding domain of the BTK molecule.[43] In CLL cell lines, ibrutinib initiates apoptosis via the caspase pathway and results in reduced MAPK, PI3K, and NF-κB signalling.[44] In addition to disrupting BCR signalling pathways, ibrutinib also affects the interaction between CLL cells and their microenvironment. For example, ibrutinib has been shown to disrupt the protective effect of stromal cells by inhibiting CD40, BAFF, Toll-like receptor, and cytokine signalling.[44] In another study, ibrutinib interfered with the homing and adhesion of CLL cells to the stroma by reducing secretion of chemokines CCL3 and CCL4 in response to BCR activation, and inhibiting CLL cell chemotaxis towards CXCL12 and CXCL13.[45] The inhibitory actions of ibrutinib on the homing of CLL cells to their microenvironment may explain the phenomenon known as redistribution lymphocytosis, which is characteristically seen during the first months of treatment with ibrutinib or idelalisib after patients show a nodal response.[43]

4.1.2. Clinical trials

Ibrutinib has produced promising results in several clinical trials of relapsed/refractory and high-risk patients with CLL. Early results from a pivotal phase Ib/II trial examining ibrutinib monotherapy in previously treated patients with CLL led to its accelerated approval by the FDA for patients with CLL who have received at least one previous therapy. In the published results from this trial, including 85 patients with previously treated CLL, ORR was 71% and response was independent of clinical and genomic risk factors, including the presence of del(17p).[46] At 26 months, the estimated PFS and OS rates were 75% and 83%, respectively. A randomized, phase III study of ibrutinib versus ofatumumab (a next-generation, fully humanized anti-CD20 monoclonal antibody) was also initiated in patients with relapsed or refractory CLL (RESONATE trial). After the first interim analysis, the response rate as determined by an independent review committee was 63% for ibrutinib (including 20% partial response with lymphocytosis), compared to 4% response with ofatumumab.[47] In addition, at a median follow-up of 9.4 months for ibrutinib, PFS was significantly prolonged in the ibrutinib arm compared with the ofatumumab arm (median PFS: not reached vs. 8.1 months, HR = 0.22 [95% CI: 0.15–0.32]; p <0.001). Importantly, this positive effect of ibrutinib was also observed in subgroups of patients with high-risk features, including del(17p) and resistance to purine analogue therapy. Based on the results from the RESONATE trial, the FDA expanded the use of ibrutinib to include patients with CLL that are positive for del(17p). Single-agent ibrutinib has also been approved by Health Canada for CLL patients who have received at least one prior therapy, or for the frontline treatment of patients with del(17p).

The safety results from these clinical trials indicate that ibrutinib is a very well-tolerated drug, with few discontinuations due to treatment-emergent adverse events (AEs) reported. Most of the AEs were grade 1 or 2, including transient diarrhea, fatigue, and upper airway infections.[48] Grade 3/4 hematologic toxicity was infrequent and consisted mostly of neutropenia (approximately 15% incidence).[46,47] In the RESONATE trial, atrial fibrillation was a serious AE reported at a higher frequency in the ibrutinib arm (ibrutinib, 10 patients; ofatumumab, 1 patient).[47] Bleeding-related AEs of any grade also occurred more frequently in the ibrutinib arm (ibrutinib, 44%; ofatumumab, 12%).

4.2. Idelalisib

4.2.1. Mechanism of action

Idelalisib is an orally bioavailable, first-in-class, isoform-selective PI3K-δ inhibitor. PI3K has four catalytic isoforms (α, β, γ, δ); the delta isoform being highly expressed in lymphoid cells.[49] As idelalisib is highly selective for PI3K-δ, patients do not experience elevations of serum glucose, insulin, or proinsulin C-peptide levels that are typical in patients receiving pan–PI3K inhibitors.[50,51] In addition, unlike pan-PI3K inhibitors, idelalisib is not cytotoxic to normal Natural Killer cells and T cells.[52] *In vitro* studies have shown that idelalisib decreases phosphorylation of AKT and extracellular signal-regulated kinase (ERK), thus disrupting BCR signalling.[52] Idelalisib also initiates apoptosis via the caspase pathway, and this was found to be independent of genomic features such as del(11q), del(17p), and immunoglobulin heavy chain variable region

(IgHV) mutational status.[53] Like ibrutinib, idelalisib was also found to antagonize survival signals initiated by CD40L, BAFF, TNF-α, and fibronectin; as well as inhibit BCR-induced secretion of CCL3 and CCL4 from CLL cells and migration of CLL cells towards the chemokines CXCL12 and CXCL13.[53,54]

4.2.2. Clinical trials

Idelalisib has demonstrated encouraging results in combination with rituximab in a phase III, randomized controlled study of patients with CLL who had progressed within 24 months after their last treatment and were considered ineligible for chemotherapy due to comorbidities, decreased renal function, or myelosuppression.[55] The population in this study was heavily pretreated and more than 40% of patients were positive for del(17p) or TP53 mutations. The trial was stopped at the interim analysis due to the overwhelming efficacy of idelalisib plus rituximab over rituximab plus placebo. The ORRs were 81% in patients who received idelalisib plus rituximab versus 13% for rituximab plus placebo. Notably, after 12 months of follow-up, patients treated with idelalisib plus rituximab had a significantly improved PFS (HR = 0.15, p <0.001) and OS (HR = 0.28, p = 0.02) compared with patients treated with rituximab plus placebo. The PFS superiority held in all subgroups analyzed, including patients with del(17p), TP53 mutations, and IgHV unmutated status.[55] Results from this study led to the FDA approval of idelalisib plus rituximab in July 2014 for patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other existing medical conditions. Health Canada has also approved idelalisib in combination with rituximab for patients with relapsed CLL.

In current clinical trials, idelalisib has demonstrated a good safety profile, and showed good tolerability in heavily pretreated patient populations. The most frequent AEs included fatigue, diarrhea, pyrexia, nausea, chills, and cough, most of which were grade 1 or 2.[51,55] The most clinically significant grade ≥3 AEs reported included pneumonia/pneumonitis, diarrhea with colitis, and alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations.[56] These AEs occur in as many as 20% of patients and are primarily observed after continued drug exposure. They are also manageable in most patients and resolve with appropriate intervention.

5. Future impact on treatment decisions

The introduction of rituximab in combination with FC has largely impacted the goals of therapy for patients with CLL. By combining targeted and non-targeted therapies with unique mechanisms of action, FCR displays additive and synergistic effects that translate to favourable response rates and prolonged PFS and OS. The new small-molecule inhibitors ibrutinib and idelalisib have been intelligently designed to target signalling pathways involved in CLL pathogenesis and are therefore expected to change the landscape of treatment for patients with CLL (Table 1). These new therapies appear to be very tolerable, even in heavily pretreated patients, suggesting that they should also be a good frontline therapy option for unfit CLL patients who are unable to tolerate

Table 1. The role of patient and disease factors on influencing treatment decisions, in the present and in the future, with the availability of new targeted agents

Factors	Present	Future
Del(17p)/TP53 mutation positive	• Standard chemotherapy-based treatments are ineffective	• Potential role of new agents (idelalisib, ibrutinib) as effective therapy for these patients
Patient fitness	• Patients can be categorized by suitability for aggressive treatment vs. less toxic therapy	• New agents with lower toxicity may be suitable for patients with a range of fitness levels
Patient preference	• Choice of intravenous vs. oral therapies given factors such as access/distance to treatment centre, mobility issues • Choice to go through more aggressive treatments	• Choice of new oral agents • Choice of new agents with high efficacy and decreased toxicity

aggressive chemoimmunotherapies. In addition, as hematologic toxicities are infrequent, these new agents may be particularly useful in relapsed patients with residual cytopenias from prior therapies. As more experience with these agents is gathered in frailer patients, it is possible that patient fitness will adopt a lesser role in influencing treatment goals in the future.

Ibrutinib and idelalisib have several additional advantages, including the convenience of oral administration. This is an important benefit for patients, giving them flexibility in the timing and location of treatment administration. Unfortunately, these agents are also provided indefinitely (until disease progression), which may lead to issues with patient adherence.

One of the most important features of these novel targeted therapies is their ability to produce substantial responses in heavily pretreated, high-risk patients, including those with del(17p) and TP53 mutations. As patients with these genetic aberrations currently have limited treatment options, the availability of new targeted agents will significantly and positively impact these patients. Although del(17p) and TP53 mutations are the only genetic markers that currently instruct treatment decisions, these genetic aberrations can only partly explain chemotherapy resistance, as TP53 disruptions are present in only about 40% of relapsed and fludarabine-refractory CLL patients.[23] Therefore, it will be important to continue to investigate the biology behind chemorefractoriness in order to identify additional subgroups of patients who may benefit from earlier access to targeted therapy.

6. Conclusions

Understanding CLL biology has led to a new generation of treatment options that promise to be (i) effective, even in patients with TP53 aberrations or heavily pretreated patients with refractory disease, and (ii) convenient and tolerable, even for elderly frail patients. A number of unanswered questions remain with the use of targeted therapies in the treatment of CLL, including which combination therapies are most effective, as well as their long-term efficacy and safety. Over the next few years, it will be exciting to watch how these new agents are incorporated into treatment algorithms and to see whether these new treatments will change the goals of therapy for a wider range of patients to include prolonged survival and maintenance of quality of life.

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