New Strategies in Chronic Lymphocytic Leukemia: Shifting Treatment Paradigms
Farrukh T. Awan and John C. Byrd

Abstract
Over the past two decades, slow but deliberate progress has been made in understanding the genetics of chronic lymphocytic leukemia (CLL) and how the surrounding microenvironment influences leukemia cell survival. The complexity of CLL with respect to different chromosomal aberrations, lack of a common aberrant signaling pathway activation, and associated immune suppression of the disease has been seen a major stumbling block for developing a single targeted therapy similar to imatinib used in chronic myeloid leukemia. The upcoming therapeutic era we are entering with the B-cell receptor (BCR) tyrosine kinase inhibitors ibritinib and idelalisib appears to be overcoming this obstacle. Indeed, for the large majority of patients, it appears that application of BCR kinase inhibitors can promote durable remissions without the need for chemotherapy. Where other very active targeted agents such as ABT-199, therapeutic antibodies, and chimeric antigen receptor–modified T-cells will be used in CLL also represents a major question that future clinical trials will answer.

Background
The advent of B-cell receptor (BCR) kinase inhibitors signals a landmark event in the management of patients with chronic lymphocytic leukemia (CLL). Kinase inhibitors are not just another treatment option for these patients but have the potential to effectively transform the treatment paradigm for this disease. Early results with these agents, including ibritinib and idelalisib, which target Bruton tyrosine kinase (BTK) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), respectively, have shown promising efficacy and excellent tolerability that allows for prolonged treatment. Moreover, discovery of novel prognostic markers and their significance with regard to disease progression and response to therapy has also improved personalized therapy for these patients (Fig. 1).

BTK was first discovered as the defective protein kinase in the inherited disease X-linked agammaglobulinemia that is characterized by a severe immune-deficient state (1). A deleterious mutation of the BTK results in severely impaired B-cell development and subsequent impaired B-cell immunity (2). Furthermore, stimulation of the BCR results in induction of tyrosine phosphorylation and activation of BTK and subsequent triggering of multiple pathways involved in B-cell survival (2). CLL B cells have been shown to have an increased level of BTK that can be activated by the autonomous BCR activation recognized in CLL B cells (3). Ibrutinib is a first-in-class, irreversible inhibitor of BTK. It covalently binds to Cys-481 in the ATP-binding domain of the BTK molecule and abrogates BCR-mediated survival signals. Ibrutinib also has the ability to irreversibly target IL2-inducible T-cell kinase (ITK) in T cells potentiating Th1-driven immune responses (4), thus potentially reversing tumor-induced T-cell anergy and providing an alternative immune-modulating role for this treatment.

Recent reports from early-phase clinical trials of ibritinib in patients with relapsed CLL have shown an overall response (OR) rate of 71% with an additional 20% of patients experiencing a partial response with lymphocytosis (PR+L). These responses were independent of conventional clinical and genetic factors and resulted in a progression-free survival (PFS) rate of 75% at 26 months (5). Similar exciting results were reported in elderly, treatment-naive patients treated with ibritinib with an OR rate of 71% and a 13% PR+L. These responses also appear to be sustained over time, with PFS of 96.1% at 2 years (6). Ibrutinib in general is well tolerated, with the most common side effects being mild diarrhea, nausea, and fatigue. Interestingly, PR+L does not appear to predict for inferior PFS (7).

PI3Ks are a family of enzymes involved in an extraordinarily diverse group of cellular functions, including cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking (8). Many of these functions relate to the ability of class I PI3Ks to activate the PI3K–AKT–mTOR pathway (9). The p110δ isoform regulates different aspects of cellular proliferation and survival and is constitutively overexpressed in CLL B cells (10). Idelalisib is an orally bioavailable, first-in-class isoform selective PI3K-δ inhibitor that promoted apoptosis of CLL B cells ex vivo.

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was also shown to be successful in abrogating the survival signal provided by the microenvironment (11).

In a recent report of a phase I trial (12), idelalisib was evaluated in patients with relapsed/refractory high-risk CLL patients and resulted in an OR rate of 72% (including PR+L). The median PFS duration was 15.8 months. Therapy was generally well tolerated, with the most commonly observed grade $\geq 3$ adverse events being pneumonia (20%), neutropenic fever (11%), and diarrhea (6%).

On the basis of these early results, multiple studies are currently under way to further improve the outcomes of patients with CLL treated with kinase inhibitors. This review focuses on the ongoing development of these agents.

On the Horizon

Chemoinmunotherapy versus kinase inhibitors

Despite the early excitement about the use of kinase inhibitors in the management of CLL, long-term data are lacking and multiple questions are still unanswered about the durability of their efficacy and long-term disease control. Early results, however, indicate that in patients with treatment-naive CLL, PFS was 96.1% at 2 years despite the lower complete response (CR) and OR rates (6). This compares extremely favorably to a failure-free survival rate of 51% at 6 years reported with the use of fludarabine, cyclophosphamide, and rituximab (FCR) chemoinmunotherapy (13). However, long-term data reported from the initial cohort of patients treated with FCR at The University of Texas MD Anderson Cancer Center (Houston, TX) reveal that patients with mutated IGHV and 13q deletion have extremely prolonged PFS with no relapses reported after 10 years (14). These issues are being addressed by two large intergroup trials currently under way to compare ibrutinib with chemoimmunotherapy as first-line treatment.

A significant issue with the use of chemotherapy has been the incidence of infectious complications. Specifically, treatment with regimens such as FCR results in prolonged significant cytopenias (grade 2–4), and resulting infectious complications ranging from 35% at 3 months to 12% at 9 months. Moreover, 38% of the patients develop infectious complications if they were cytopenic at 9 months (15). Fludarabine-based regimens are also poorly tolerated in patients above 65 to 70 years of age, in those with multiple comorbid conditions, and in patients with impaired renal function. These findings are in contrast with data reported from the ibrutinib trials that demonstrate a progressive decline in the incidence of infectious complications with ongoing therapy (5) with excellent tolerability in...
older patients and patients with comorbidities. This may preclude routine antimicrobial prophylaxis commonly used with chemoimmunotherapy. Moreover, improvements were also observed in stress, depressive symptoms, fatigue, and quality of life in patients treated with ibrutinib (16); factors that are generally adversely affected while patients are undergoing chemotherapy. Likewise, a combination of idelalisib and rituximab was also found to be safe and effective in patients with compromised renal function and comorbid conditions (17).

Chemotherapy, especially when nucleoside analogues are combined with alkylating agents, is associated with a significant rate of therapy-related secondary malignancies in up to 35% of patients, and more importantly, therapy-related myeloid neoplasms in up to 10% of patients (13, 15, 18). Current follow-up of ongoing studies with kinase inhibitors is too short to draw definitive conclusions about the risks of secondary malignancies in patients who will be exposed to these agents for an extended period. These effects would need to be evaluated in ongoing post-approval studies.

Early results from combinations of kinase inhibitors with targeted therapies such as rituximab have also been encouraging. The combination of ibrutinib and rituximab in patients with high-risk CLL was generally well tolerated and resulted in an OR rate of 95% and a PFS rate of 78% at 18 months (19). However, patients did experience a higher incidence of atrial fibrillation and bleeding diathesis possibly due to collagen-mediated platelets aggregation defect (20, 21). Similarly, the combination of idelalisib and rituximab resulted in an OR of 81% and PFS in 1 year in excess of 90%. Serious toxicities observed with idelalisib included transaminase elevations, diarrhea with colitis, and pneumonitis that were primarily observed after continued drug exposure (12).

The question of whether kinase inhibitors will replace chemotherapy as first-line treatment for patients with CLL remains to be answered, but a vast majority of patients are likely to consider or to be prescribed oral kinase inhibitors as these agents become more acceptable in the oncology community. These agents are more likely to be used in combination with other targeted therapies, and patient and cost preference will probably dictate a limited treatment course.

Establishing endpoints for kinase inhibitor therapy

Another issue that might become more relevant in the future is the duration of therapy with kinase inhibitors. No consensus currently exists for the appropriate endpoint of therapy with kinase inhibitors. There is also no validated clinical or laboratory endpoint that might be used as a surrogate for a stopping rule. Minimal residual disease (MRD) status has been established as a marker for predicting survival in patients treated with kinase inhibitors (17) and is likely to be used for making treatment discontinuation decisions. However, because monotherapy with kinase inhibitors has not been shown to result in MRD-negative states, various combinations with different targeted therapies are being explored to achieve MRD-negative status and potentially limit the duration of therapy and possibly the emergence of resistance to kinase inhibitors. Early results with ibrutinib in combination with rituximab show a small percentage of patients with MRD-negative disease at 12 months of therapy (22), supporting an argument for combining targeted therapies with kinase inhibitors to effect a deeper remission.

Kinase inhibitors in patients with high-risk CLL

Outcomes in patients with high-risk del(17p) CLL are an area of special interest because these patients have rapidly progressive disease and limited effective therapeutic options. Recently reported FCR data reveal an OR rate of 33% with a median PFS duration of 14 months in this group of patients (23). Various other agents, including alemtuzumab (24) and rituximab (25) in combination with high-dose steroids and oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR; ref. 26), flavopiridol (27), and lenalidomide (28)–based combinations result in similar response rates and short PFS.

Early data from ibrutinib in patients with del(17p) reveal an OR rate of 55.9% with a median duration of response of 25 months. Ibrutinib was also well tolerated, with gradual decline in the incidence of adverse events with progressive therapy (29). Our institutional historical comparison also revealed a significantly improved response rate and PFS when ibrutinib was compared with either cyclin-dependent kinase inhibitors or other conventional therapies (30). Similar exciting results have been preliminarily reported in patients treated with a combination of idelalisib and rituximab with OR rates around 80% and PFS at 1 year in excess of 75% (17). However, despite the fact that therapy with kinase inhibitors may result in improved response as compared with conventional therapies, the outcomes of patients with these high-risk mutations are still inferior to those for patients without these abnormalities. These findings suggest that kinase inhibitors are not able to completely overcome the adverse prognosis conferred by the presence of these factors (5). Efforts are currently under way to further improve outcomes in patients in this high-risk group by using various combinations of kinase inhibitors with targeted therapies.

Kinase inhibitors in the initial treatment of high-risk patients not meeting criteria for therapy

The International Workshop on Chronic Lymphocytic Leukemia (IWCLL; ref. 31) recommends initiating therapy for CLL at the onset of symptoms or documentation of clinically significant progressive disease. This recommendation is based on historical data that failed to demonstrate a survival advantage with early treatment of patients with CLL (32). Recent attempts to treat patients early with high-risk disease on clinical trials were halted because of poor accrual. However, these treatments were primarily based on chemoimmunotherapeutic regimens with associated toxicities. Given the excellent tolerability and impressive responses observed in patients treated with kinase...
inhibitors, efforts are currently under way to evaluate the role of these agents in patients with high-risk disease at the time of diagnosis before they meet the conventional criteria for initiating therapy. This approach has the potential to significantly prolong overall survival of patients with CLL, and early disease control might limit the development of immune dysfunction and resulting infectious complications, which are the leading cause of morbidity and mortality in patients with CLL (33).

Resistance to kinase inhibitors and strategies to overcome it

Chronic exposure to kinase inhibitors might result in clonal selection pressure resulting in the emergence of resistant malignant cell clones. Recent data derived from whole-exome sequencing of paired samples at baseline and at the time of relapse during treatment with ibrutinib identified a cysteine-to-serine mutation in BTK at the binding site of ibrutinib and three distinct mutations in phospholipase Cγ2 (PLCγ2; ref. 34). Functional analysis revealed that the C481S mutation of BTK results in a protein that is only reversibly inhibited by ibrutinib. The R665W and L845F mutations in PLCγ2 are both potentially gain-of-function mutations that lead to autonomous BCR activity. Trials are under way of innovative BTK inhibitors that bind to an alternative site in the BTK protein and may potentially be effective in patients who acquire resistance to ibrutinib through the binding site mutation. Interestingly, these mutations were not found in any of the patients with prolonged lymphocytosis who were taking ibrutinib, suggesting an alternative and as yet unidentified mechanism for the persistence of lymphocytosis in those patients. Efforts are currently under way to identify specific resistance mechanisms to other novel therapies and kinase inhibitors. This will enable us to develop specific agents that have the ability to overcome these resistance pathways and eventually develop therapeutic protocols that can be used in combination at the outset and limit the development of these resistance mechanisms.

New frontiers

Multiple therapies are currently at various stages of development for the treatment of patients with CLL. These include alternative kinase inhibitors, including spleen tyrosine kinase (SYK; ref. 35), cyclin-dependent kinase (CDK; ref. 36), and others; antibodies and antibody such as molecules targeting various surface antigens on CLL B cells, including CD20 (37), CD19 (38, 39), and CD37 (40), etc. and various other molecules specifically designed either to directly target CLL B cells or overcome the microenvironmental signals that provide the CLL B cells a survival advantage, for example, ABT-199 (41) and lenalidomide (28).

One of the most significant advances in the treatment of patients with CLL has been the development of autologous chimeric antigen receptor–modified T cells directed toward the CD19 antigen (42). Autologous lentiviral-modified T cells were able to persist in vivo for an extended period and were able to induce prolonged clinical responses in the majority of patients (42, 43). Therapy was, however, associated with significant cytokine release syndrome necessitating intensive supportive care (44, 45). Moreover, treatment resulted in the elimination of normal B cells and subsequent sustained hypogammaglobulinemia. Aggressive supportive care and infection prophylaxis can limit the incidence of infectious complications in these patients and result in prolonged disease control. Larger multi-institutional trials are currently under way to further develop and enhance this potentially curative therapy.

Therapy for CLL has undergone remarkable progress over the last few years with multiple new agents being approved by the FDA or in the process of obtaining approval. The majority of these agents are generally well-tolerated oral agents with remarkable efficacy. Together with antibodies and kinase inhibitors (21), various combinations of these therapies have the potential to transform care of patients with CLL and potentially affect the ever-elusive cure with limited adverse effects.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: F.T. Awan, J.C. Byrd
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F.T. Awan, J.C. Byrd
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F.T. Awan, J.C. Byrd
Writing, review, and/or revision of the manuscript: F.T. Awan, J.C. Byrd
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.C. Byrd
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