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REVIEW ARTICLE

Entering the Era of Targeted Therapy for Chronic Lymphocytic Leukemia: Impact on the Practicing Clinician

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ABSTRACT

Purpose
Chemoimmunotherapy has been the standard of care for chronic lymphocytic leukemia (CLL). However, the introduction of B-cell receptor (BCR) kinase inhibitors such as ibrutinib has the potential to eliminate the role of chemotherapy in the treatment of CLL. How to best incorporate old and new therapies for CLL in this landscape is increasingly complex.

Methods
This article reviews current data available to clinicians and integrates these data to provide a strategy that can be used to approach the treatment of CLL in the era of BCR signaling inhibitors.

Results
Current strategies separate patients based on age or functional status as well as genetics [presence or absence of del(17)(p13.1)]. In the era of targeted therapy, this will likely continue based on current available data. Phase III studies support chemoimmunotherapy as the initial standard therapy for patients without del(17)(p13.1). Choice of chemotherapy (fludarabine plus cyclophosphamide, bendamustine, or chlorambucil) and anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) varies based on regimen and patient status. For patients with del(17)(p13.1), no standard initial therapy exists, although several options supported by phase II clinical trials (methylprednisolone plus alemtuzumab or ibrutinib) seem better than chemoimmunotherapy. Treatment of relapsed CLL seems to be best supported by ibrutinib-based therapy. Completion of trials with ibrutinib and other new agents in the near future will offer opportunity for chemotherapy-free treatment across all groups of CLL.

Conclusion
Therapy for CLL has evolved significantly over the past decade with introduction of targeted therapy for CLL. This has the potential to completely transform how CLL is treated in the future.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) occurs most frequently in patients age > 70 years and is similar genetically to small lymphocytic lymphoma (SLL), where blood lymphocytosis is lacking. The natural history of CLL progression is variable and influenced in great part by genetic, epigenetic, and biochemical properties of the tumor cells and clinical features at time of diagnosis. On the basis of earlier studies demonstrating no benefit of early treatment with alkylator-based therapy, treatment of CLL is not recommended until symptoms develop.[1] However, during the past 5 years, the application of genomic studies and introduction of many new therapies for CLL have greatly increased the complexity of treating symptomatic CLL.[2,3] In addition, new targeted therapy offers the possibility of a paradigm shift in this disease. This review focuses briefly on the biology of highly promising targets that are being pursued and expands on treatment scenarios clinicians will encounter as we enter the new era of targeted therapy for CLL.

RELEVANT THERAPEUTIC TARGETS FOR CLL

Extensive basic scientific investigation over the past three decades has begun to unravel different immunologic, biochemical, and genetic features of malignancies, including CLL, that offer opportunity for therapeutic targeting. Outlined here are pathways relevant to CLL for which impactful therapies are emerging.

B-Cell Receptor Signaling and Microenvironment

Antigen-dependent and -independent B-cell receptor (BCR) signaling plays a central role in the pathogenesis of CLL (Fig 1).[4,5] In addition, BCR

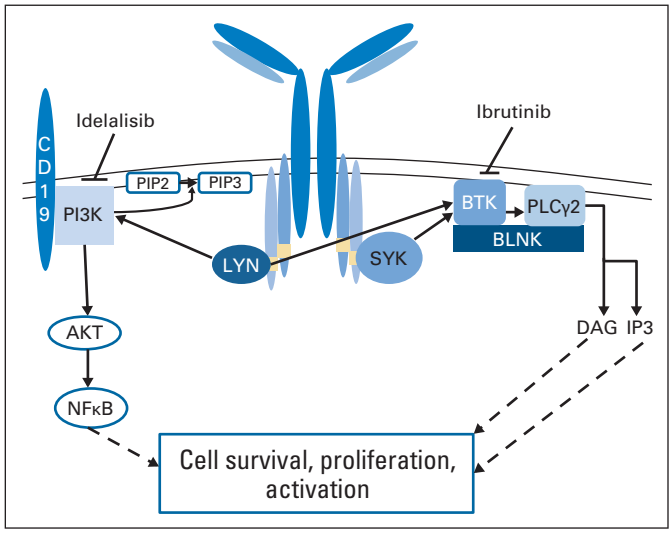

Fig 1. Simplified model of B-cell receptor signaling. Pathways demonstrated are actively targeted by therapeutic agents currently under late development or in postmarketing evaluation for chronic lymphocytic leukemia. BTK, Bruton's tyrosine kinase; PI3K, phosphatidylinositide 3-kinase.

signaling activates integrin signaling and enhances CLL cell adhesion to microenvironment stroma, thereby increasing resistance to apoptosis.[6,7] BCR signaling in CLL is not driven by a specific mutation or rearrangement but instead by amplification of several survival pathways, including phosphatidylinositide 3-kinase (PI3K), NF-κB, and MAPK/ERK, which are constitutively active in the lymph node and bone marrow compartments of CLL, where disease expansion occurs.[8] Although many of the components of BCR signaling are ubiquitous and therefore challenging to therapeutically target, mouse knockout or inactivation studies of both PI3Kδ and Bruton's tyrosine kinase (BTK) have demonstrated a predominately B-cell phenotype.[9-11] These findings, combined with strong preclinical studies showing that inhibitors of p110δ PI3K[12-14] and BTK[7,15-17] prevent BCR-mediated proliferation, stromal protection, and signaling, provide justification for study of these agents in CLL. The two most mature therapeutic agents coming forward—idelalisib and ibrutinib—differ considerably from each other not only in target but also in mechanism. Idelalisib is a selective and reversible inhibitor of PI3Kδ,[14] whereas ibrutinib irreversibly inactivates BTK by forming a covalent bond with a cytsteine residue (C481). Ibrutinib also inhibits several other kinases (interleukin-2–inducible T-cell kinase [ITK], TEC, BMX, EGFR, and HER4) with a similar cysteine-binding residue near the ATP binding pocket of the kinase.[17]

Immune Dysfunction

One of the paramount ways cancer establishes itself is through suppressing both the acquired and innate immune systems. Immune suppression in CLL leads to disease progression, infection, and secondary malignancies and occurs through multiple mechanisms, including expansion of T regulatory cells, depression of antibody production, skewing of T cells toward a Th2 phenotype, and suppression of natural killer (NK) – cell and monocyte function.[18-20] Immune dysregulation associated with CLL is present early in the disease and worsens in parallel with disease-related symptoms.[20] Compounding this issue is that many of the therapies used in CLL, including fludarabine[21,22] and bendamustine,[23,24] are profoundly immune suppressive. Specific targeting of immune dysfunction in CLL is possible with lenalidomide, a multitargeted therapeutic now recognized to enhance E3 ubiquitin ligase degradation of Ikaros 1 and 3, the former of which represses interleukin-2 production, thereby enhancing T-cell and NK-cell activation and function.[25] Lenalidomide also inhibits T regulatory cells[26] and has been shown in several studies to promote T-cell synapse toward CLL cells.[27,28] Passive use of immune therapy in CLL with monoclonal antibodies such as rituximab, when combined with chemotherapy, prolonged survival in this disease.[29-31] Refinements in CD20 antibody properties have resulted in US Food and Drug Administration approval of two new antibodies (ie, ofatumumab and obinutuzumab). Similarly, although specifically developed to inhibit BCR signaling, the PI3Kδ inhibitor idelalisib likely has immune modulatory function through inhibition of T regulatory cells,[32] and the BTK inhibitor ibrutinib was demonstrated by our group to also inhibit ITK.[33] ITK is an essential kinase for immunosuppressive Th2 CD4 T cells, and therefore, ibrutinib skews CD4 T cells back to a Th1 phenotype, which responds more appropriately to infection or malignancy. Thus, it seems that many of the targeted therapies currently being explored in CLL directly or indirectly influence disease-associated immune suppression.[33]

Other Therapeutic Targets

Cell survival in CLL is currently targeted through BCL2 and MCL1. ABT263, which inhibits BCL2 function, has demonstrated dramatic clinical activity with durable remissions as part of phase I studies in relapsed CLL.[34] A second-generation molecule more selective for BCL2 inhibition, ABT-199, lacks BCL-XL as a target and is currently in clinical trials with CLL.[35] The dose-limiting toxicity of ABT-199 has been hyperacute tumor lysis syndrome, which has slowed development of this exciting compound but seems to be manageable with careful dose escalation. Therapeutics targeting MCL1 specifically are not currently available, but alternative therapeutics that inhibit gene transcription via CDK9 inhibition, such as pan-CDK inhibitors (eg, flavopiridol and dinaciclib), are clinically active in CLL and also have the dose-limiting toxicity of tumor lysis syndrome.[36] Similarly, therapeutics targeting CD37 and promoting SHP1 activation, which inhibits BCR signaling, are also under study.[37,38] However, because these agents are farther from regulatory approval, they will not be discussed in our review, which focuses solely on current treatment modalities employed for CLL.

SYMPTOMATIC, UNTREATED ELDERLY PATIENTS

Despite chlorambucil being an accepted therapy for elderly patients with CLL, transition to more superior combination therapy of either chlorambucil or bendamustine with rituximab has occurred (Table 1). New data on alternative CD20 antibodies and chlorambucil have also been reported, as summarized here.

Bendamustine Chemoimmunotherapy

The Gynecologic Cancer Study Group (GCSG) CLL2M study represents the largest phase II study of bendamustine published and included 117 previously untreated patients with CLL who were treated with bendamustine plus rituximab (BR).[39] Treatment was administered every 28 days for up to six cycles. The median age of patients was

Table 1. Completed Treatment Trials Relevant to Untreated Elderly Patients With CLL

Treatment	Phase	No. of Patients	ORR (%)	CR Rate (%)	Median PFS (months)	del(17)(p13.1) Worse
CLB plus rituximab	II	100	82	9	24	Yes
CLB plus rituximab	II	97	82.4	18.9	34.7	Yes
Bendamustine plus rituximab	II	117	88	23	33.0	Yes
Ibrutinib	IB/II	31	71	13	96%*	Unknown
Idelalisib plus rituximab	IB/II	64	97	19	93%*	Unknown
CLB *v*	III	221	69	1	13.1	Unknown
CLB plus ofatumumab		226	82	12	22.4	
CLB *v*	III	118	31.4	0	11.1	Yes
CLB plus rituximab *v*		330	65.3	7.3	16.3	
CLB plus obinutuzumab		333	77.3	22.3	26.7	

Abbreviations: CLB, chlorambucil; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; PFS, progression-free survival.
*At 24 months.

64 years; 26% were age > 70 years; 46% had Binet stage C disease. The overall response rate (ORR) was 88%, and the complete response (CR) rate was 23%. Median event-free survival with this treatment was 33 months. Patients of all genomic groups except for del(17)(p13.1) responded favorably; for those with del(17)(p13.1), we do not recommend this treatment. Treatment was generally well tolerated, with cytopenias and infections being most problematic. Treatment-related mortality was 4%, mostly as a consequence of infections. The safety of this regimen in older patients was retrospectively confirmed in another study examining outcome in elderly patients treated with bendamustine.[40] Although prospective randomized phase III data examining BR in this population do not exist, BR represents an acceptable initial treatment for elderly patients with CLL lacking del(17)(p13.1).

Chorambucil Chemoimmunotherapy

Several phase II trials have demonstrated the favorable efficacy and safety of the combination of chlorambucil and rituximab.[41,42] These trials ultimately formed the basis for studying chlorambucil chemoimmunotherapy as part of two phase III trials in elderly untreated patients with CLL administered second-generation CD20 antibodies.

The first trial (COMPLEMENT 1 [Ofatumumab Plus Chlorambucil Versus Chlorambucil Monotherapy in Previously Untreated Patients With Chronic Lymphocytic Leukemia]), which has only been preliminarily reported, used ofatumumab, a type 1 humanized CD20 antibody that has a different binding site than rituximab and is much more effective than rituximab at complement mediation, direct killing with crosslinking, and antibody-dependent cellular cytotoxicity (ADCC).[43] The trial examined the efficacy of adding ofatumumab to chlorambucil in patients for whom fludarabine therapy was inappropriate based on age or comorbidities.[44] A total of 447 patients were enrolled, with a median age of 69 years; 82% were age ≥ 65 years and/or had ≥ two comorbidities. The combination arm had a significantly higher ORR (82% *v* 69%), CR rate (12% *v* 1%), and progression-free survival (PFS; median, 22.4 *v* 13.1 months) as compared with those receiving chlorambucil. The frequency of grade ≥ 3 adverse events occurred in 50% of patients receiving the combination treatment and 43% of patients receiving chlorambucil alone, with the most common events being neutropenia (26% *v* 14%), infection (15% *v* 14%), and infusion toxicity (10%, all in combined arm). No survival advantage was noted after short follow-up.

The second trial (GCSG CLL11) focused on the value of adding either rituximab or obinutuzumab to chlorambucil.[45] Obtinutuzumab is a type 2 CD20 human antibody that is glycoengineered to enhance NK cell–mediated ADCC. This large phase III study did not use age as an eligibility criterion; rather, it used a high cumulative illness rating scale score, which denotes functional comorbidity, or modestly impaired renal function (glomerular filtration rate, 30 to 69 mL/min). The study showed that combination therapy yielded a significantly higher ORR (77.3% *v* 31.4%), CR rate (22.1 *v* 0%), PFS (median, 26.7 *v* 11.1 months), and overall survival (OS; death rate, 9% *v* 20%) as compared with chlorambucil. Only the subset of patients with del(17)(p13.1) did not benefit from this combined therapy. The combination of obinutuzumab plus chlorambucil was also statistically superior to that of rituximab plus chlorambucil with regard to ORR (78.6% *v* 65.1), CR rate (20.7% *v* 7%), and PFS (median, 26.7 *v* 15.2 months). No survival advantage was noted after short follow-up. The efficacy of the obinutuzmab combination is further exemplified by the significantly higher frequency of bone marrow minimal residual disease (MRD) negativity (obinituzumab, 19.5% *v* rituximab, 2.6%). Grade 3 and 4 infusion-related events were more frequent and severe with obinutuzumab (20% *v* 4%) than with rituximab, but in all cases, they were manageable. Similarly, grade 3 and 4 neutropenia was higher with obinutuzumab (33% *v* 28%) as compared with rituximab, but no increased risk in serious infections was noted. Overall, this study represents a major advance in the treatment of elderly patients with CLL lacking del(17)(p13.1) and establishes one standard of care for both elderly patients and those with comorbid conditions that make aggressive chemoimmunotherapy unfeasible.

Ibrutinib Therapy

Ibrutinib is an oral irreversible inhibitor of BTK that has demonstrated significant efficacy in relapsed CLL with durable remissions, including in patients with del(17)(p13.1), with modest toxicity. Limited data suggest even more impressive efficacy in previously untreated patients with CLL. A study of 31 patients age ≥ 65 years were treated with ibrutinib 420 mg daily until progression or unacceptable toxicity. The median age was 71 years, and more than half of patients had advanced Rai stage disease.[46] Only 9% of patients had high-risk genomic features, either del(11)(q22.3) or del(17)(p13.1). The ORR according to 2008 International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria was 71%, and an additional 13% of patients achieved partial responses (PRs) with lymphocytosis. At a median follow-up of 24 months, PFS and OS rates were 96%. Toxicity was similar to that observed in patients treated for relapsed disease.[47] These results are quite remarkable, but they only applied to predominately low–genomic risk patients. These promising data prompted several ongoing phase III trials of ibrutinib in the elderly (summarized in Table 2), which have the potential to change CLL treatment recommendations in the future. RESONATE II (A Multicenter, Open-Label, Phase III Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765

Table 2. Ongoing Phase III Studies With Potential to Change Standard of Care in CLL

Study	Treatment Comparison	Treatment Status	Age Group (years)
CLL12	Ibrutinib *v* placebo	High risk, aymptomatic	≥ 18
RESONATE II	CLB *v* ibrutinib (crossover)	Symptomatic, untreated	≥ 65
A041202	BR *v* ibrutinib plus rituximab *v* ibrutinib (crossover)	Symptomatic, untreated	≥ 65
E1912	FCR *v* IR	Symptomatic, untreated	< 70
NCT01980888	BR plus placebo *v* BR plus idelalisib	Symptomatic, untreated	≥ 18
NCT01980875	Idelalisib plus rituximab *v* placebo plus rituximab or idelalisib plus CLB *v* placebo plus CLB	Symptomatic, untreated	≥ 65
CLLM1	Lenaldiomide *v* placebo for consolidation after initial therapy	Consolidation after first treatment	≥ 18
RESONATE	Ofatumumab *v* ibrutinib	Relapsed	≥ 18
NCT01611090	BR plus placebo *v* BR plus ibrutinib	Relapsed	≥ 18
NCT01569295	BR plus placebo *v* BR plus idelalisib	Relapsed	≥ 18
NCT02005471	ABT199 plus rituximab *v* BR	Relapsed	≥ 18

Abbreviations: BR, bendamustine plus rituximab; CLB, chlorambucil; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphophamide, and rituximab; IR, ibrutinib plus rituximab; RESONATE, A Phase III Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia; RESONATE II, A Multicenter, Open-Label, Phase III Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.

Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma), which has completed enrollment, includes patients age ≥ 65 years and is comparing chlorambucil with ibrutinib in previously untreated CLL, with a primary end point of PFS. If durable remissions with ibrutinib are confirmed in this trial, this will likely become an acceptable therapy for patients with CLL. The Alliance A041202 trial, which is actively accruing patients, will compare chemoimmunotherapy (BR) with either ibrutinib or ibrutinib plus rituximab in patients age ≥ 65 years and represents the first comparison of chemoimmunotherapy with ibrutinib-containing regimens in elderly patients.

Other Therapies

Other agents potentially used include lenalidomide with or without rituximab, which in several phase II trials demonstrated responses and durable remissions in the majority of patients. Long-term follow-up in one study demonstrated minimal long-term toxicity with follow-up exceeding 4 years.[48,49] A phase III study examining chlorambucil versus lenalidomide in elderly patients was terminated early because of early deaths in patients age > 80 years and likely futility in obtaining the study primary end point. Lenalidomide represents one of the only therapeutics used in CLL that is immune restorative, but unfortunately, current data do not support its initial use for CLL therapy outside the setting of a clinical trial. Similarly, idelalisib has been explored predominately in relapsed CLL. However, a phase IB study has been preliminarily reported in elderly treatment-naive patients treated with eight doses of rituximab once per week in combination with idelalisib administered continuously at 150 mg twice per day until progression.[50] Outcome in this preliminary report included data on 50 patients, demonstrating an ORR of 97% (CR rate, 19%). PFS rate at 24 months was 93%, including all nine patients with del(17)(p13.1) or *p53* mutation. Many patients discontinued therapy because of diarrhea or other nonhematologic toxicities, and only 45% continue to receive idelalisib maintenance. Further follow-up is required to determine the duration of remission and feasibility of this regimen for patients receiving continuous idelalisib therapy.

Table 3. Select Chemoimmunotherapy Trials Relevant to Untreated Young Patients With CLL

Treatment	Phase	No. of Patients	ORR (%)	CR Rate (%)	Median PFS (months)	del(17p) Worse
Fludarabine → rituximab *v*	II	51	77	28	42	Yes
FR		53	90	47	42	
FCR	II	300	85	72	80	Yes
BR	II	117	88	23	33.0	Yes
Pentostatin, cyclophosphamide, and rituximab	II	64	91	41	32.6	Yes
FC *v*	III	31	88.4	21.8	32.8	Yes
FCR			95.1	44.1	51.8	
FCR *v*	III	284	97.8	47.4	85%	Yes
BR		280	97.8	38.1	78.1%	

Abbreviations: BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukemia; CR, complete response; FC, fludarabine plus cyclophosphophamide; FCR, fludarabine, cyclophosphophamide, and rituximab; FR, fludarabine plus rituximab; ORR, overall response rate; PFS, progression-free survival.

SYMPTOMATIC, UNTREATED YOUNGER PATIENTS

The genesis of treatment for younger patients with CLL has changed modestly over the past two decades. However, the addition of the CD20 antibody rituximab to either FR[51] or FR plus cyclophosphamide (FCR)[30] in two separate phase II studies with extended follow-up seemed to prolong survival over historical controls. Table 3 summarizes relevant trials.

Fludarabine Chemoimmunotherapy

The promising studies with FR[51] and FCR[30] prompted a large phase III study (GCSG CLL8) that enrolled 761 previously untreated patients with CLL, with random assignment between FC and FCR.[31] This study reported an ORR (95.1% *v* 88.4%), CR rate (44.1% *v* 21.8%), PFS (median, 51.8 *v* 32.8 months), and OS rate (alive, 87% *v* 83%) that were statistically superior with FCR. Emerging from this study were numerous biologic correlative studies showing the most predictive test of long-term PFS and OS was attainment of MRD-negative disease by high-sensitivity flow cytometry. In addition, patients with unmutated *IGHV* disease had a shorter PFS and OS with

both FCR and FR, although rituximab seemed to benefit both treatment groups. All interphase cytogenetic groups benefited from rituximab, with exception of those with del(17p13.1) and patients with no interphase cytogenetic abnormalities. Toxicity included regimen-related mortality of 2%, with cytopenias and infections being the most common causes of morbidity. Long-term follow-up presented at the IWCLL meeting in 2013, from both this study and the MD Anderson Cancer Center FCR experience, suggests that durable remissions seem to occur, with the appearance of a plateau lacking late relapses in patients with *IGHV*-mutated disease with favorable interphase cytogenetics [ie, del(13)(q14) and trisomy 12]. For this subset of patients with CLL, treatment with FCR seems most advantageous, because the potential to induce durable remissions exists. Although this favorable patient group also does well with FR-based chemoimmunotherapy, the extended remissions observed with FCR and current absence of randomized data showing similar outcomes with attenuated therapy support use of the FCR regimen.

Bendamustine Chemoimmunotherapy

Attempts to improve on the early and late toxicities observed with FCR have been a recent major focus of research in younger previously untreated patients with CLL. In addition to the data on BR we mentioned earlier in this article, the GCSG performed a phase III study (CLL10) comparing BR with FCR in fit patients with CLL. The preliminary outcomes have been presented, demonstrating inferior response and PFS with BR as compared with FCR[52] across all genetic groups. On the basis of these results, the GCSG still considers FCR to be its standard therapy for young, fit patients with CLL.

PUTTING IT ALL TOGETHER FOR SYMPTOMATIC, UNTREATED PATIENTS: WHAT IS BEST?

The completion of several phase III studies has advanced therapy for CLL across several different ages, functional statuses, and genomic groups. Reliance on therapies shown to prolong survival in CLL represents the best standard therapeutic option. For older patients lacking del(17)(p13.1), strong consideration should be given to initial treatment with obinutuzumab plus chlorambucil or BR, unless a confounding comorbidity exists prohibiting this. The use of ibrutinib in this population is limited, and recommendations will best be made once RESONATE II is completed. For younger, more fit patients lacking del(17)(p13.1), consideration of FCR-based therapy seems most justified at the present time. With this therapy, assessment of bone marrow MRD-negative status offers the opportunity for extended remission and justifies this procedure after therapy. Patients with significant disease burden after completion of FCR treatment should be considered for clinical trials targeting elimination of MRD.

CLINICAL APPROACH FOR SYMPTOMATIC PATIENTS WITH DEL(17)(p13.1)

Although representing only 7% to 10% of patients with symptomatic previously untreated CLL, those with del(17)(p13.1) present perhaps the most challenging treatment decisions. There is no clear consensus among experts as to the best therapy for this patient group. Cytotoxic chemotherapy is much less effective, and the addition of CD20 antibody therapy does not significantly affect outcome. Treatment regimens using high-dose steroids with alemtuzumab, which have resulted in higher ORRs, CR rates, and PFS rates than expected with chemotherapy, have been put forward as an alternative, but outcomes remain suboptimal.[53] To date, results with ibrutinib in this patient population in the relapse setting have been the most promising,[54] although they are still limited. Given the improved toxicity profile of ibrutinib over high-dose steroids and alemtuzumab, this might represent the best available option for these patients. However, enrollment onto clinical trials should be of highest priority for this patient group. The role of allogeneic transplantation as part of consolidation therapy for those with del(17)(p13.1) should be considered as one option, particularly in younger patients, if a good donor exists. However, the durable remissions observed with ibrutinib have called into question this recommendation if other effective cytoreductive therapy is available should relapse of disease occur.

TREATMENT OF RELAPSED CLL

In many regards, the approach to relapsed CLL is similar to the evaluation before initial therapy. Treatment initiation should not occur until patients are symptomatic and meet one of the defined criteria for treatment. It is important to repeat interphase cytogenetics to evaluate clonal evolution, which may direct therapy decisions. Bone marrow biopsy should be repeated in patients with cytopenias, especially in patients who have received FCR, because therapy-related myeloid neoplasm (trMN) occurs more commonly in this group. Identification of coexisting trMN generally prompts immediate consideration of disease cytoreduction as appropriate and allogeneic stem-cell transplantation if a donor exists, because of poor outcomes in these patients and challenges in treating coexisting CLL and trMN. Although a host of therapies exists for relapsed CLL (outlined in National Comprehensive Cancer Network guidelines),[55] recent trials with ibrutinib suggest it to be the best initial choice for this patient population.

Ibrutinib Therapy

Ibrutinib has shown exceptional activity in relapsed CLL. A phase I study of ibrutinib in relapsed B-cell malignancies was initiated, where durable clinical activity was noted in nine of 16 patients with CLL or SLL.[56] Notable among these patients with CLL receiving ibrutinib was early lymphocytosis, which now is recognized to be a class effect of all BCR antagonists. This occurs early with therapy but is otherwise accompanied by reduction in organomegaly, lymph node size, and cytopenias, thereby differentiating it from typical progression seen with chemoimmunotherapy. No dose-limiting toxicity was identified with ibrutinib at any dose. This study was followed by a phase IB/II study of ibrutinib, where 85 patients with relapsed or refractory CLL or SLL were treated at two different doses (420 and 840 mg daily).[54] This group was heavily pretreated (median, four prior therapies) and had a high proportion of patients with advanced-stage disease and del(17)(p13.1). Similar to the phase I study of ibrutinib, an early increase in lymphocytosis was typically noted by day 7 and persisted for 2 to 3 months before slowly declining over time, concomitant with notable reduction in lymph node size, spleen size, and improvement in cytopenia. The ORR by IWCLL 2008 criteria[57] was 71% (CRs, two; PRs, 34) in the 420-mg cohort and 71% (PRs, 24) in the 840-mg cohort. In addition, 10 (20%) and five patients (15%) in the 420- and

840-mg cohorts, respectively, demonstrated a nodal response with persistent lymphocytosis. A subsequent report examining outcomes of patients with persistent lymphocytosis using a landmark analysis did not demonstrate adverse outcomes in this group as compared with those with a PR or better response.[58] Response to ibrutinib did not vary based on cytogenetic adverse features previously identified in CLL. Most notably, of the 28 patients with del(17)(p13.1) enrolled onto this study, 18 (68%) responded. The 26-month estimated PFS rate for all patients enrolled onto this study was 75%. Unlike response, PFS did differ by genomic group; 26-month estimated PFS rate was 56% when either del(11)(q22.3) or del(17)(p13.1) was present versus 93% when neither of these abnormalities was present.

Extended therapy with ibrutinib was well tolerated in this trial, with common adverse events including grade 1 to 2 diarrhea, cough, fatigue, upper respiratory infections, nausea, fever, peripheral edema, myalgias, and petechiae or ecchymoses. Although grade ≥ 3 infections occurred frequently in this study, the occurrence decreased with time, where the average rate per 100 patient-months within the first 6 months was 7.1 but 2.6 thereafter. Most problematic was the low frequency of subarachnoid hemorrhages in several patients receiving concomitant warfarin treatment but no other anticoagulants or antiplatelet agents. This unusual, atypical CLL toxicity prompted prohibition of concurrent therapy with oral vitamin K antagonists in all subsequent studies of ibrutinib. In addition, ibrutinib is typically held for 3 to 7 days before and after surgical procedures in a further attempt to avoid bleeding problems. BTK does not seem essential for platelet activation, but a role for BTK inhibition in stable thrombus formulation has been postulated.[59] Studies of platelet function in patients with BTK-inactivating mutations have demonstrated abnormalities of collagen- and collagen-related peptide–induced aggregation[60] but not bleeding.[61] Sorting out the role of ibrutinib in these low-frequency toxicities will require randomized phase III trials with standard therapies in this patient population.

These results demonstrating durable remissions prompted initiation of a large randomized phase III study (RESONATE) comparing ibrutinib monotherapy with ofatumumab in patients with relapsed CLL (Table 2). This trial was recently ended by the data safety and monitoring committee because of the significant benefit seen in both PFS and OS with ibrutinib. On the basis of these collective results, ibrutinib represents the best salvage therapy for relapsed CLL irrespective of genomic risk type unless long-term anticoagulation with warfarin is required. At the present time, data support continuous use of ibrutinib in the absence of progression or toxicity.

Ibrutinib Combination Therapy

The success of ibrutinib monotherapy has prompted several combination trials, in which ibrutinib is administered with therapeutic monoclonal antibodies (eg, rituximab and ofatumumab), chemotherapy (eg, FCR and BR), and select targeted immune therapies (eg, lenalidomide). Of the studies presented to date, combination approaches have generally yielded improved ORRs in part through earlier resolution of persistent lymphocytosis.[62-64] However, none of these studies were randomized, and it is unclear if combination therapy will affect response duration versus single-agent therapy. Therefore, at the present time, the combination of ibrutinib with other therapies should not be considered outside of a well-designed clinical trial. Such trials should be directed at inducing MRD-negative CRs to facilitate cessation of therapy or alternatively at preventing resistance in the small subset predisposed to this, such as patients with del(17)(p13.1), del(11)(q22.3), or a complex karyotype.

Idelalisib Therapy

The initial phase I study with idelalisib enrolled 54 patients with relapsed or refractory CLL who were treated with continuous dosing until progression.[65] Like with ibrutinib, early lymphocytosis was observed concomitantly with reduction in nodal size. After a median 9 months of drug exposure, the ORR was 39%, with nodal response observed in a larger proportion of patients (81%). The median PFS was 17 months. Dose-limiting toxicities were not observed, and potentially treatment-related adverse events (chiefly fatigue, rash, diarrhea, respiratory tract infections, and reversible elevations of hepatic transaminases) resulted in discontinuation of treatment in only 7% of patients. Subsequent combination studies with rituximab, bendamustine, BR, ofatumumab, and chlorambucil were performed, demonstrating all these approaches resulted in higher ORRs and acceptable toxicity.[66] Several phase III studies were initiated, including combination approaches with BR, ofatumumab, and rituximab. The only fully published study administered rituximab with idelalisib or placebo as part of salvage therapy.[67] This study was closed prematurely because the combination therapy demonstrated a significantly higher ORR (81% *v* 13%), PFS rate, and OS rate at 12 months (92% *v* 80%). Grade 3 diarrhea, rash, and liver function abnormalities were more common with the combination therapy. Although idelalisib is not yet approved for marketing, it is likely that its use will be more limited based on reported shorter duration of remission with the single agent compared with ibrutinib in patients with relapsed CLL with or without del(17)(p13.1). However, market approval is anticipated, and the role of idelalisib in CLL therapy will require further follow-up.

QUESTIONS POSED BY TARGETED THERAPY

As CLL therapy evolves from chemoimmunotherapy to integrate targeted therapy, several questions arise, for which there are few extant data to guide practitioners. Although data are insufficient to make definitive statements, our experience in treating more than 300 patients with ibrutinib or other related BCR signaling agents in CLL allows us to make preliminary comments.

When Should Allogeneic Transplantation Be Considered?

For most patients with CLL who relapse after chemoimmunotherapy, reduced-intensity allogeneic stem-cell transplantation is considered. Given that all patients with CLL without del(17)(p13.1) have a 2-year relapse risk $\leq 25\%$ with ibrutinib, our practice has been to perform relevant preliminary evaluation and education regarding transplantation but not to pursue this unless other therapies are unavailable for cytoreduction in the rare event ibrutinib proves ineffective. However, if patients demonstrate progression with ibrutinib, our practice is always to immediately consider stem-cell transplantation after cytoreduction. Patients with both untreated and relapsed del(17)(p13.1) disease have a 57% 2-year PFS rate and present a more challenging transplantation decision. If transplantation is pursued in this setting, we generally treat with ibrutinib for 1 year to increase the depth of remission before transplantation to avoid rapid tumor flare, which can occur with early cessation of this agent. In addition, an

exciting modality that will also be explored for these patients is chimeric antigen T-cell (CAR-T) therapy, which does not require an allogeneic donor. Preliminary activity with CAR-T therapy has been reported in CLL with demonstrated therapeutic efficacy.[68] Although cytokine release and tumor lysis syndromes have been observed in the short term, and long-term hypogammaglobulinemia has followed, there is no risk of acute or chronic graft-versus-host disease with this treatment. Integrating ibrutinib with this approach represents an exciting potential opportunity for future clinical investigation.

How Should Patients With Ibrutinib Resistance Be Managed?

Ibrutinib relapse generally occurs in the context of Richter's transformation and, less commonly, CLL progression. In general, progression is manifested by persistent increasing enlargement of lymph nodes or rising lymphocyte count with ibrutinib therapy. Clinicians must use caution in assigning progression to intermittent mild excursions in lymphocyte counts or node size, because these can occur in some patients and do not represent progression. Similarly, transient cessation of ibrutinib because of surgical procedures, infections, or other causes can sometimes cause flare of node size, cytopenia, or lymphocytosis, which quickly resolves with reinstitution of therapy. In most cases of CLL relapse and some cases of Richter's transformation, mutations of either the *BTK* gene at the C481 residue, where the drug irreversibly binds, or the *PLCGγ2* gene, the immediate downstream target of BTK, are found.[69] Cessation of ibrutinib therapy in relapsing patients can sometimes result in rapid tumor progression, particularly for patients with previously heavily treated CLL or Richter's transformation. Therefore, our practice is not to discontinue ibrutinib therapy until immediately before the next treatment is initiated. In our experience thus far, patients with CLL with ibrutinib progression have been responsive to other CLL therapies. In contrast, the outcome of Richter's transformation after ibrutinib is poor; responses to other therapies, including investigational agents, have been observed but have often been of brief duration. Allogeneic stem-cell transplantation for Richter's transformation of CLL at any time point in the disease should be strongly considered.

DISCUSSION

After multiple decades of incremental therapeutic advances, new targeted therapies offer the opportunity to revolutionize the treatment of CLL. With new and more effective targeted and immune-directed therapies, it is possible that CLL therapy in the near future for most patients will evolve into treatment that does not involve chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOSSARY TERMS

BCR: B-cell antigen receptor that is a prerequisite for antigen recognition by B cells and for generation of a specific antibody immune response. BCR signaling is involved in the pathogenesis of several B-cell malignancies.

BTK (Bruton's tyrosine kinase): a B-cell signaling kinase best known for its involvement in B-cell receptor (BCR) signaling. BTK mutations are the cause for X-linked agammaglobulinemia, a rare primary immunodeficiency.

ibrutinib: an irreversible BTK inhibitor.

minimal residual disease (MRD): the low level of tumor cells (eg, after chemotherapy) that can only be detected with highly sensitive molecular methods (eg, polymerase chain reaction) or to molecularly defined relapse after long-term remission.

PI3K (phosphatidylinositol-3 phosphate kinase): adds a phosphate group to PI3, which is a downstream signaling molecule involved in survival/proliferative pathways mediated by growth factors such as the epidermal growth factor and the platelet-derived growth factors. PI3K is a heterodimeric molecule composed of a regulatory subunit and a catalytic subunit.

Th2: a categorization of helper ($CD4^+$) T-cell responses, manifested typically by production of cytokines, including interleukin-4, interleukin-5, and interleukin-10, and with functional importance in supporting generation of B-cell and antibody responses.