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Advancements in the Treatment of B-Cell Malignancies

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Target Audience

The educational design of this activity addresses the needs of oncologists, hematologists, oncology nurses, and oncology researchers involved in the treatment of patients with B-cell malignancies.

Statement of Need/Program Overview

Analysis of the clinical data, treatment guidelines, and ongoing clinical trials in hematology/oncology has revealed a professional practice gap in the area of those physicians charged with treating hematologic malignancies, including lymphoma and leukemia and in particular with respect to B-cell malignancies. These gaps impact knowledge, competence, and performance. This gap is mainly due to the current speed and "breakneck" pace at which B-cell malignancies research is progressing. Hematologists and oncologists find it difficult to stay apprised of the latest results and need direction as to how to incorporate them into clinical practice. Beyond the agents and technologies currently being developed, the Food and Drug Administration has approved several drugs for B-cell malignancies since 2008.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe recent advances in the current understanding of the biology of B-cell malignancies including aberrant cell signaling pathways.
- Compare current and emerging treatment strategies for patients with B-cell malignancies.
- Discuss evidence produced by recent studies on investigational therapies or regimens for treatment of some prevalent B-cell malignancies.

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Susan O'Brien, MD
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B-Cell Receptor Pathway Inhibitors—Rationale and Potential

John G. Gribben, MD, DSc, FMedSci

The B-cell receptor (BCR) pathway is fundamentally important in the proliferation, survival, and homing of normal and malignant B cells (Figure 1). This complex process involves numerous signaling molecules that are activated or inhibited as a result of BCR activation. Elucidation of key components of this pathway has identified new therapeutic targets for the treatment of B-cell malignancies.

The BCR complex consists of the antigen-specific immunoglobulin (Ig) in association with Igα/Igβ heterodimers (CD79A/CD79B). Recognition of specific extracellular antigens by the surface BCR activates the BCR signaling pathway, resulting in phosphorylation of the immunoreceptor tyrosine-based activation motifs (ITAMS) located in the intracellular domains of CD79A/CD79B. This phosphorylation event recruits the protein tyrosine kinase spleen tyrosine kinase (SYK), which leads to the activation of the Src family kinases. This event results in activation of Bruton's tyrosine kinase (BTK), a protein that is required for BCR signaling. Activation of Src family kinases also results in activation of phosphoinositol-3 kinase (PI3K), which then activates the nuclear factor kappa-B (NF-κB) and mitogen-activation protein (MAP) kinase pathways.

Targeted agents have been developed against several BCR-associated kinases, including SYK, BTK, and PI3K. Some of these agents are still in preclinical development, and others have demonstrated significant activity in clinical trials. These potent agents have been shown to inhibit the corresponding signaling pathways and alter migration patterns of lymphoma cells, perhaps making them more susceptible to cell killing.

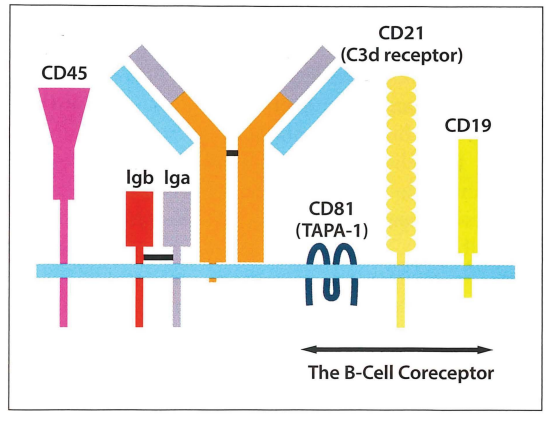


Figure 1. The B-cell receptor pathway is fundamentally important in the proliferation, survival, and homing of normal and malignant B cells.

New BCR Pathway Inhibitors

Clues to the function of BTK were provided by the observation that individuals with a congenital deficiency in BTK lack B cells and antibodies. BTK is critical for

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lymphoma cell survival and proliferation. Several BTK inhibitors are being evaluated in clinical trials; the furthest in development is ibrutinib, a tyrosine kinase inhibitor (TKI) that forms a specific, irreversible bond with a cysteine reductase in BTK.[1] Ibrutinib is administered orally once daily. Other BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules within those cells. Ibrutinib has not demonstrated toxicity against T cells or natural killer cells, although off-target signaling through other kinases may occur.

Ibrutinib has been shown to induce apoptosis of lymphoma cells. It also inhibits chemokine-induced migration of chronic lymphocytic leukemia (CLL) cells into the tumor microenvironment (Figure 2).[2] This inhibition promotes migration of CLL cells into the circulation, where they may be more susceptible to cell killing. In addition, it causes a rebound lymphocytosis after initial administration, which has created challenges for assessing responses to therapy. Although the effect of ibrutinib on CLL cell migration has been observed in both IgG-mutated and IgG-unmutated cases, clearance of cells from the periphery occurs more rapidly in IgG-unmutated CLL, suggesting that these cells may rely more heavily on the tumor microenvironment for survival and highlighting a potential therapeutic strategy for these aggressive tumors.[3]

Ibrutinib has demonstrated activity in a variety of B-cell malignancies, including indolent non-Hodgkin lymphoma (NHL), CLL, and mantle cell lymphoma (MCL). Clinical trials are ongoing. The addition of other agents such as rituximab or bendamustine to ibrutinib has been shown to reduce the duration of lymphocytosis. Additional clinical trials are needed to determine whether a quicker response improves clinical outcomes.

Several PI3K inhibitors in development target different isoforms of this important signaling molecule. Idelalisib is a highly selective inhibitor of PI3-kinase δ, an isoform that is highly restricted to lymphocytes. Idelalisib inhibits proliferation, induces apoptosis, and inhibits homing and retention of malignant B cells.[4] Idelalisib has also demonstrated activity in a variety of B-cell malignancies.

PI3K inhibitors have also been developed that target other PI3K isoforms; these agents include a γδ inhibitor and pan-PI3K inhibitors. Other investigational TKIs inhibit multiple pathways; one example is an inhibitor of PI3-kinase/mammalian target of rapamycin (mTOR).

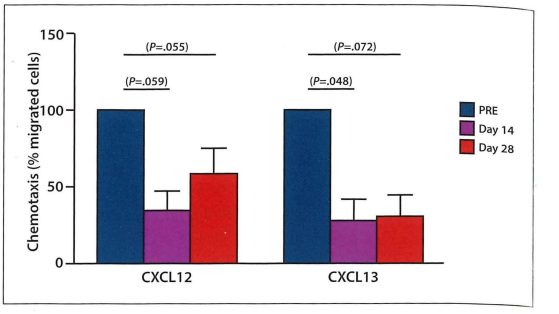


Figure 2. Ibrutinib inhibits chemokine-induced migration of chronic lymphocytic leukemia (CLL) cells into the tumor microenvironment. Adapted from Hoellenriegel J. *Blood* (ASH Annual Meeting Abstracts) 2012;120(21): Abstract 186.

Clinical trials are needed to determine the most effective method of inhibiting PI3K to optimize activity against B-cell malignancies.

Overall, BCR signaling inhibitors have demonstrated significant single-agent activity in a variety of B-cell malignancies, highlighting the dependence of many B-cell malignancies on these signaling pathways. Moreover, the observation that normal B cells are often less affected by BCR signaling inhibitors than are malignant cells suggests that B-cell malignancies rely on these signaling pathways for survival. Thus, a fuller understanding of these pathways and their dysregulation in B-cell malignancies may identify other potential therapeutic targets to be explored.

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The Potential for Eliminating Chemotherapy in Indolent Non-Hodgkin Lymphoma

Bruce D. Cheson, MD

Chemotherapy has evolved considerably since injectable mustard gas was first used as cancer therapy. Although chemotherapy has become more effective and, in some cases, less toxic, it is still associated with nonspecific effects, including acute and long-term toxicity. Targeted agents have provided an alternative to chemotherapy that often involves less toxicity to healthy cells. Combinations of targeted agents have demonstrated activity comparable to chemotherapy or chemoimmunotherapy, making the possibility of chemotherapy-free regimens a potential reality.

Monoclonal Antibody–Based Therapy

The possibility of a chemotherapy-free regimen for indolent lymphoma was explored nearly a decade ago, when Ghielmini and colleagues demonstrated prolonged remissions with rituximab monotherapy (375 mg/m^2 weekly for 4 weeks) followed by rituximab maintenance therapy (375 mg/m^2 every 2 months for up to 4 doses) in patients with follicular lymphoma.[1] After a median follow-up of 35 months, the prolonged rituximab regimen was associated with a median event-free survival (EFS) of 36 months in chemotherapy-naive patients. After 8 years, 45% of previously untreated patients who responded to rituximab induction and received extended rituximab remained progression-free.[2]

Czuczman and colleagues conducted a phase 2 trial of the anti-CD80 monoclonal antibody galiximab plus rituximab in 61 patients with previously untreated follicular lymphoma.[3] The Follicular Lymphoma International Prognostic Index (FLIPI) score correlated with outcomes (Figure 3). The overall response rate (ORR) was 92% (75% complete responses [CR]) in patients with a FLIPI score of 0 to 1, 80% (48% CR) in patients with a FLIPI score of 2, and 55% (27% CR) in patients with a FLIPI score of 3 to 5. After a median follow-up of 4.3 years, the median PFS was 2.9 years, with outcomes again varying by FLIPI score. The regimen was well tolerated, with minimal toxicity.

Rituximab has also been evaluated in combination with the anti-CD22 monoclonal antibody epratuzumab. In a phase 2 study of previously untreated patients with follicular lymphoma, 59 evaluable patients received rituximab (375 mg/m^2 weekly for 4 weeks then every 8 weeks for 4 additional doses) and epratuzumab (360 mg/m^2 given 2 days before the first rituximab dose then on the same day as each subsequent rituximab dose).[4] The regimen was associated with an ORR of nearly 90% and has demonstrated durable responses.

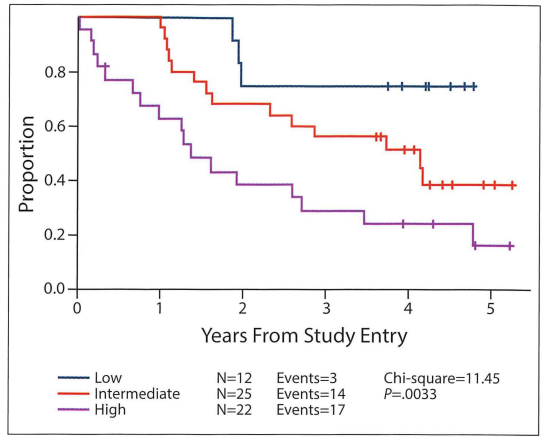


Figure 3. Progression-free survival by FLIPI score in the Cancer and Leukemia Group B 50402 study, a phase 2 trial of galiximab plus rituximab in patients with previously untreated follicular lymphoma. FLIPI, Follicular Lymphoma International Prognostic Index. Adapted from Czuczman MS, et al. *Ann Oncol.* 2012;23:2356-2362.[3]

Antibody-Drug Conjugates

Antibody-drug conjugates physically link a monoclonal antibody to a cytotoxic agent, providing targeted delivery of the cytotoxic agent directly into the target cell. The antibody-drug conjugate inotuzumab ozogamicin consists of the anti-CD22 antibody linked to calicheamicin. After inotuzumab ozogamicin demonstrated antitumor responses in a phase 1 study,[5] a combination of inotuzumab ozogamicin and rituximab was evaluated in a phase 1/2 study in patients with relapsed or refractory CD20-positive, CD22-positive B-cell NHL, including 39 patients with follicular lymphoma. Patients received rituximab plus inotuzumab every 4 weeks for up to 8 cycles. In the subset of patients with follicular lymphoma, the regimen was associated with an ORR of 87% and a 2-year progression-free survival (PFS) rate of 68%. The most common grade 3/4 adverse events in the overall patient population were thrombocytopenia

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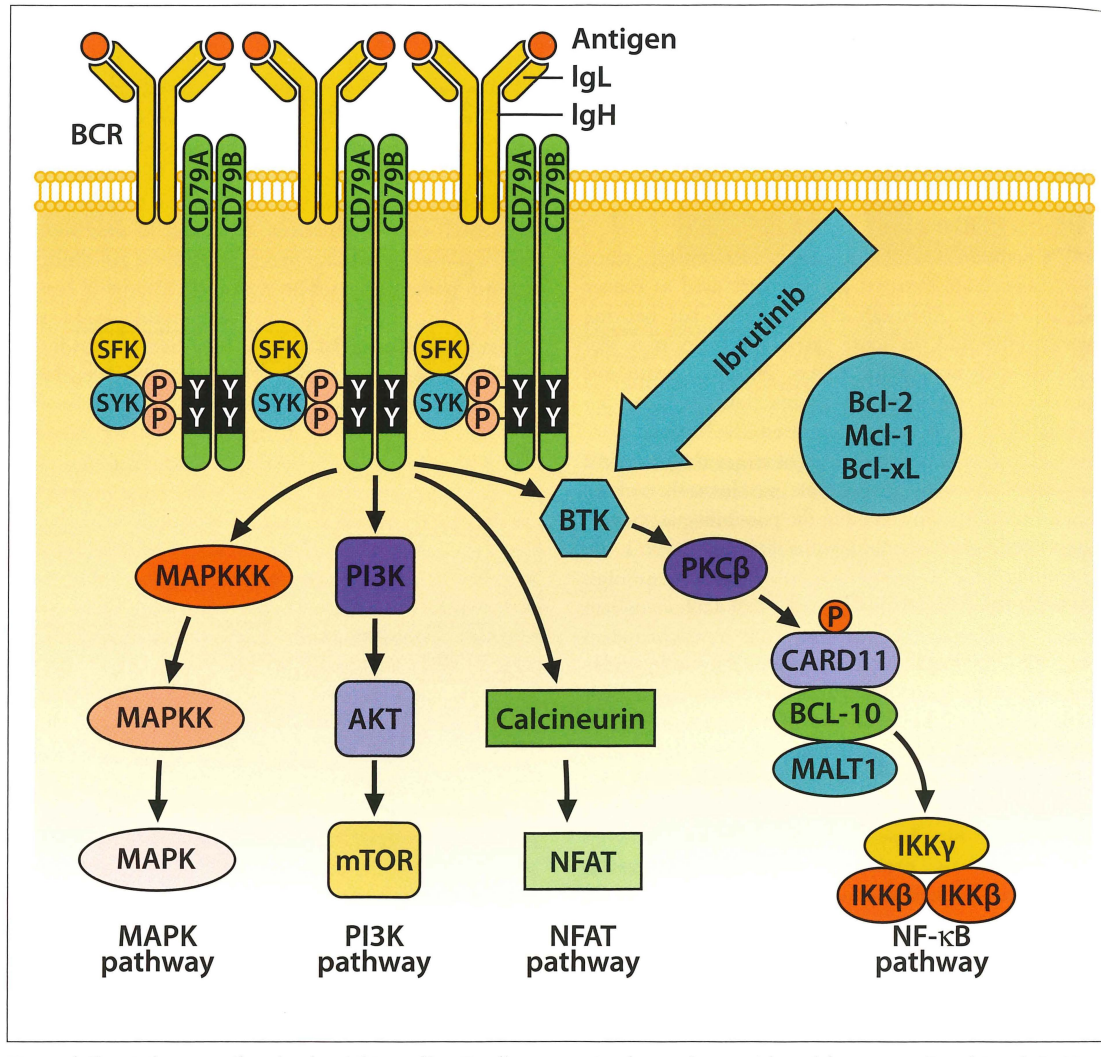


Figure 4. Ibrutinib is a small-molecule inhibitor of key B-cell receptor signaling pathways. Adapted from Young R and Staudt L. *Nat Rev Drug Discov.* 2013.[21]

(31%) and neutropenia (22%). Other common adverse events of any grade included elevated aspartate aminotransferase (AST; 36%) and hyperbilirubinemia (25%).

Several other antibody-drug conjugates are currently in development for B-cell malignancies. Two compounds are being developed that use monomethyl auristatin E (MMAE) as the cytotoxic agent; this agent is the same one used in the highly active anti-CD30–containing antibody-drug conjugate brentuximab vedotin. Antibody-drug conjugates under development include one linking anti-CD22 and MMAE and another linking anti-CD79b and MMAE. Phase 1 studies demonstrated antitumor activity with both of these novel antibody-drug conjugates alone or with rituximab in patients with relapsed/refractory B-cell NHL.[6,7]

The ongoing randomized, phase 2 ROMULUS (A Study of DCDT2980S in Combination With MabThera/Rituxan or DCDS4501A in Combination With MabThera/Rituxan in Patients With Non-Hodgkin's Lymphoma) trial is comparing rituximab plus the anti-CD22–containing conjugate versus rituximab plus the anti-CD79b–containing conjugate in patients with follicular lymphoma and diffuse large B-cell lymphoma.[8] Patients with a response to the assigned therapy remain on that therapy until disease progression, at which point they cross over to the other arm. Patients with no response to initial therapy also cross over to the other arm. The trial will thus evaluate the relative efficacy of these approaches and the potential cross-resistance of the 2 antibody-drug conjugates.

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BCR-Targeting Small-Molecule Inhibitors

Several small-molecule inhibitors of key BCR signaling pathways have been evaluated alone and as components of combination therapy in the treatment of B-cell malignancies. In a dose-ranging phase 1 study, the BTK inhibitor ibrutinib (Figure 4) demonstrated antitumor activity in patients with various relapsed/refractory B-cell malignancies.[9] Among the 16 enrolled patients with follicular lymphoma, single-agent ibrutinib was associated with an ORR of 44%, including 19% CRs, a median response duration of 12.3 months, and a median PFS of 13.4 months. There were no dose-limiting events reported. An ongoing phase 2 study is further evaluating the efficacy and safety of ibrutinib in the treatment of follicular lymphoma.

The PI3Kδ inhibitor idelalisib (formerly CAL-101) has also been evaluated in the treatment of B-cell malignancies. A phase 1 dose-ranging study in treatment-experienced patients with a variety of NHL subtypes demonstrated a high response rate and durable tumor control at doses of at least 100 mg twice daily.[10] For both ibrutinib and idelalisib, use of a dose that attains full occupancy appears to be important for obtaining maximal antitumor activity.

Based on the outcomes in single-agent studies, both ibrutinib and idelalisib are being evaluated as components of combination therapy. A phase 1 study evaluating idelalisib in combination with rituximab, bendamustine, or both showed promising activity, with treatment up to 2.5 years in some patients, and no unexpected toxicities.[11] In this early study, the inclusion of bendamustine did not appear to provide additional benefit over rituximab, suggesting that chemotherapy could be omitted from this regimen. Phase 3 trials evaluating idelalisib with rituximab or bendamustine plus rituximab are under way.

The PI3K γ- δ-specific inhibitor IPI-145 has also demonstrated early activity in B-cell malignancies, including in patients with indolent lymphoma.[12] An expansion cohort is currently enrolling to further evaluate the activity and safety of IPI-145.[13]

Agents Targeting the Apoptosis Pathway

A variety of agents are also being developed that target proteins involved in apoptosis, including BCL2 family members and DR4/DR5. ABT-199 is a potent, selective Bcl-2 inhibitor that has demonstrated activity and acceptable toxicity in a phase 1 study of patients with relapsed NHL.[14] The best dose and schedule of ABT-199 have not yet been identified.

Immunomodulatory Drugs

The immunomodulatory drug lenalidomide, which is now approved by the US Food and Drug Administration (FDA) for use in relapsed or refractory MCL, is also being evaluated in a variety of other B-cell lymphomas. The randomized phase 2 Cancer and Leukemia Group B (CALGB) trial 50401 was initially designed as a 3-arm trial comparing rituximab, lenalidomide, or both in patients with relapsed follicular lymphoma after at least 1 rituximab-based regimen. The rituximab-alone arm closed because of slow accrual, and results from the remaining 2 arms were presented in 2012.[15] Of the 94 evaluable patients, 45 were assigned to lenalidomide and 44 were assigned to lenalidomide plus rituximab. The combination regimen appeared to be more effective than lenalidomide alone, with ORRs of 72.7% (36.4% CR) and 51.1% (13.3% CR), respectively, and a median EFS of 2.0 and 1.2 years, respectively (P=.010; Figure 5).

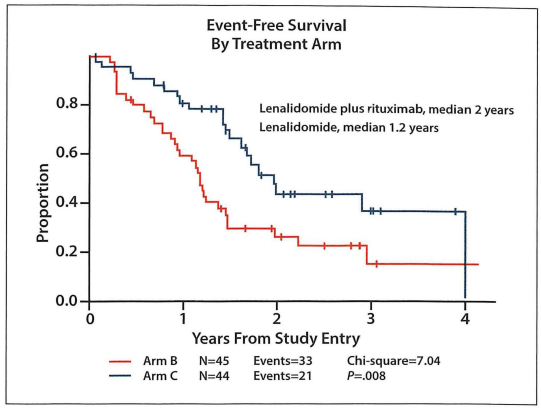


Figure 5. In the Cancer and Leukemia Group B 50401 trial, the combination of lenalidomide plus rituximab was associated with improved event-free survival compared with lenalidomide alone. Data from Leonard J et al. *J Clin Oncol.* 2010;30(15S): Abstract 8000.[15]

The combination of lenalidomide and rituximab has been evaluated in other clinical trials in indolent lymphoma. In a phase 2, multicenter trial by Martin and coworkers in patients with previously untreated follicular lymphoma, the combination was associated with an overall response of 92.6%, including 72.2% CRs and 20.4% partial responses (PRs).[16] In a single-institution study, Fowler and colleagues evaluated lenalidomide plus rituximab for up to 12 months in patients with previously untreated indolent lymphoma.[17] The doublet therapy was associated with a high response rate, including 98% (87% CR) in follicular lymphoma, 89% (67% CR) in marginal zone lymphoma, and 80% (27% CR) in small lymphocytic leukemia. Although median PFS has not yet been reached, outcomes appear favorable.

The international, randomized RELEVANCE (Combined Rituximab and Lenalidomide Treatment for Untreated Patients With Follicular Lymphoma) trial is comparing rituximab plus lenalidomide induction therapy, followed by rituximab plus lenalidomide maintenance therapy, versus rituximab plus chemotherapy (investigator's choice of

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R-CHOP, R-CVP, or bendamustine plus rituximab) followed by rituximab maintenance.[18] This trial has the potential to substantially change the treatment of follicular lymphoma.

Novel Combinations

Early trial results with novel agents have led to the design of a variety of trials evaluating new combinations for the treatment of indolent lymphoma. The Alliance for Clinical Trials in Oncology is sponsoring 2 studies. One trial is evaluating a 3-drug regimen of rituximab, lenalidomide, and ibrutinib (A051103) in patients with previously untreated follicular lymphoma.[19] The other is evaluating rituximab, lenalidomide, and idelalisib in relapsed/refractory follicular NHL patients already treated with at least 1 anti-CD20–based regimen (A051202).[20]

In summary, approaches to the treatment of B-cell malignancies have been moving away from nonspecific cytotoxic chemotherapy toward the use of agents that specifically target molecules and processes important to cancer cell growth and survival. Although not all of these newer agents have significant single-agent activity, they may be highly effective when used in rational combinations based on biological mechanisms relevant to the malignancy. Thus, the optimal therapeutic strategy is likely to differ across lymphoma subtypes, which tend to be biologically heterogeneous. Therapy will likely become more individualized. With the number of agents under active investigation, it will be important to accrue sufficient numbers of patients on clinical trials to fully evaluate these agents. These strategies may lead to the elimination of chemotherapy, in at least some cases, and increase the potential for cure.

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The Changing Landscape in CLL

Susan O'Brien, MD

Chemoimmunotherapy-based treatment approaches such as fludarabine, cyclophosphamide, and rituximab (FCR) have improved outcomes for patients with CLL. However, these regimens are not well tolerated in older patients and are associated with substantial myelotoxicity. Moreover, most patients eventually relapse after chemoimmunotherapy, and there is a lack of effective treatment options for relapsed patients. Newer BCR-targeted agents are being evaluated in the treatment of CLL, including BTK inhibitors and PI3K inhibitors.

Single-Agent Ibrutinib

The safety and activity of the BTK inhibitor ibrutinib in CLL were assessed in a phase 1b/2 trial that evaluated single-agent therapy in 31 treatment-naive patients at least 65 years of age and in 85 patients with relapsed/refractory CLL or small lymphocytic lymphoma (SLL). Outcomes in both cohorts were reported in 2012,[1] and outcomes for the patients with relapsed/refractory CLL were published in 2013.[2] Patients in the relapsed/refractory cohort had received at least 2 prior therapies (median, 4), including a purine analogue, or had high-risk disease, defined as having relapsed within 2 years of receiving combination chemoimmunotherapy or having the poor-risk genetic feature del(17p) (35%). After safety data indicated that ibrutinib was not associated with myelosuppression, the trial was opened to patients regardless of hematologic function. Therefore, there was a significant rate of cytopenias at baseline in the relapsed/refractory population. Patients were assigned to 1 of 5 cohorts in which they received ibrutinib at fixed doses of 420 mg or 840 mg daily until disease progression.

In the treatment-naive cohort, ibrutinib was associated with an ORR of 68%, including 10% CR. An additional 13% of patients had a *partial response with lymphocytosis* (Figure 6), a term used to describe patients with a dramatic reduction in lymph nodes but with concomitant lymphocytosis, which would qualify as progressive disease under the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria.[3] In the relapsed/refractory and high-risk cohort, the ORR was 70% (2% CR), and an additional 18% of patients had PRs with lymphocytosis (also called a *nodal response*). Response rates were similar across subgroups, including age, disease stage, and the presence of adverse prognostic factors. In patients with cytopenias at baseline, ibrutinib was associated with improvements in hemoglobin and platelet counts. In some cases, these improvements allowed patients to discontinue blood transfusions.

After 26 months, the estimated PFS rate was 96% for treatment-naive patients and 75% for patients with relapsed/refractory disease. Estimated OS rates at 26 months were 96% for treatment-naive patients and 83% for patients with relapsed/refractory disease. Median PFS and OS had not been reached. Notably, in both cohorts, a subset of patients remained with unresolved lymphocytosis. The promising outcomes observed in the relapsed/refractory population compare favorably to historical outcomes with the anti-CD20 antibody ofatumumab, the last agent to receive FDA approval in CLL.[4]

Ibrutinib was well tolerated, and most adverse events were grade 1 or 2. The most common adverse event was diarrhea (54%), which typically did not require medication and was often self-limiting with continued treatment. Other adverse events included fatigue (29%), upper respiratory tract infection (29%), rash (28%), nausea (26%), and arthralgia (25%).

Overall, these data demonstrated the substantial efficacy of ibrutinib in CLL patients who were treatment-naive and in relapsed/refractory CLL patients, including those with high-risk features.

Ibrutinib and Rituximab

It has been hypothesized that the addition of rituximab to ibrutinib may reduce the lymphocytosis associated with ibrutinib and accelerate responses. Therefore, a phase 2 study was undertaken evaluating ibrutinib plus rituximab in patients with high-risk CLL.[5] A total of 40 patients received ibrutinib 420 mg once daily plus weekly rituximab (375 mg/m^2) for weeks 1 to 4, then monthly until cycle 6. Daily single-agent ibrutinib was continued until disease progression or unacceptable toxicity. The median age of enrolled patients was 65 years, and patients had received a median of 2 prior therapies.

The addition of rituximab to ibrutinib appeared to reduce the lymphocytosis; lymphocyte redistribution peaked early and showed a shorter duration compared with ibrutinib alone. At the time of the analysis, response data were available at 3 to 6 months. They indicated high early response rates. The regimen was well tolerated, with most

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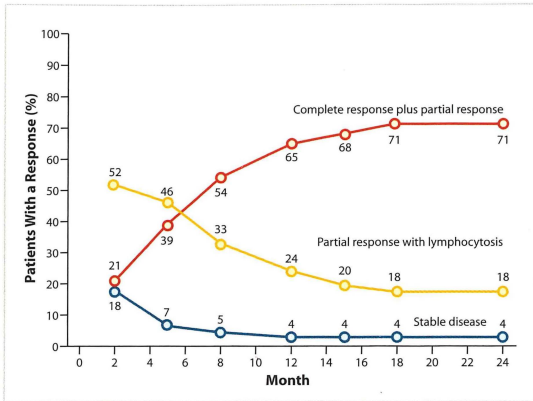


Figure 6. In a phase 1b–2 trial of ibrutinib in relapsed chronic lymphocytic leukemia, treatment-naive patients achieved an overall response rate of 68%, including 10% complete responses. An additional 13% of patients had a *partial response with lymphocytosis*, which refers to patients who had greater than 50% shrinkage of nodal disease and who fulfilled all criteria of partial response except for a persistent lymphocytosis. Adapted from Byrd JC et al. *N Engl J Med.* 2013;369(1):32-42.[2]

grade 3/4 adverse events transient and largely unrelated to the treatment. Longer follow-up is needed to further evaluate the efficacy of this combination for inducing deeper and/or more durable responses.

BTK Inhibitor CC-292

The BTK inhibitor CC-292 (previously called *AVL-292*) is also being evaluated for the treatment of CLL. A phase 1 dose-escalation study evaluated CC-292 in patients with relapsed/refractory B-cell malignancies, including patients with CLL or small lymphocytic leukemia (SLL).[6] A twice-daily dosing schedule was evaluated to address the potential production of new BTK that could have occurred between daily doses. In early follow-up, twice-daily dosing appeared to be more effective, perhaps with more rapid responses. CC-292 appeared to retain activity in patients with adverse prognostic factors, including cytogenetics. CC-292 was generally well tolerated, and most adverse events were grade 1 or 2.

Idelalisib

Idelalisib (GS-1101) is a potent, specific PI3Kδ inhibitor that, similar to ibrutinib, has been shown to antagonize BCR-triggered migration of CLL cells, inhibiting chemotaxis and retention within the stroma.[7] A phase 1 dose-ranging study was undertaken evaluating idelalisib in patients with relapsed/refractory CLL.[8]

In this phase 1 study, most patients had a lymph node response, defined as a reduction in target nodal lesions by at least 50%. Idelalisib was also associated with improvements of baseline cytopenias, including thrombocytopenia and anemia.[8] This study demonstrated significant efficacy with idelalisib in a heavily pretreated population.

The toxicity profile of idelalisib differs substantially from that of ibrutinib. The most frequently reported adverse events of any grade in the phase 1 trial were fatigue, diarrhea, pyrexia, and cough. The most common grade 3/4 adverse events were pneumonia and diarrhea. Idelalisib was associated with liver function test abnormalities, including elevations of AST and alanine transaminase (ALT). In general, these laboratory abnormalities can be addressed with dose interruptions and reductions.

After a small study demonstrated a high ORR with a combination of idelalisib plus rituximab in patients with relapsed/refractory CLL,[9] a larger study was undertaken to evaluate this combination in a different patient population. In this study, treatment-naive patients ages 65 or older with CLL or SLL received rituximab 375 mg/m^2 weekly for 8 weeks and idelalisib 150 mg twice daily for 48 weeks, followed by an optional extension study.[10] Approximately 27% of patients had anemia or thrombocytopenia at baseline, and 14% of patients had a del(17p) or TP53 mutation.

The combination of idelalisib and rituximab was associated with a high ORR and 24-month PFS. Responses occurred rapidly, and B symptoms resolved by week 16 in most affected patients. Responses also appeared to be durable, as there was no on-study progression.

Notably, the combination of idelalisib and rituximab in treatment-naive patients was associated with more toxicity than was observed with idelalisib alone in relapsed/refractory patients. Grade 3 or higher diarrhea and transaminase elevations occurred at a higher frequency in the combination arm.

It has been suggested that the increased toxicity may reflect the patient population more than the addition of rituximab, as the same degree of toxicity was not observed in the phase 1 study of idelalisib and rituximab in previously treated patients.[9] It has been proposed that some of the toxicity may be T cell–mediated, and may relate to greater immune function in the treatment-naive patient population. In some cases, the diarrhea has been managed with treatment interruptions and budesonide, allowing patients to resume therapy.

In summary, BCR inhibitors offer the advantage of oral administration and have demonstrated excellent tumor bulk reduction and an ability to improve cytopenias. These agents have demonstrated efficacy even in high-risk patients and are easily combined with other agents. They have varying adverse event profiles but are not myelosuppressive, suggesting that combination with chemotherapy could be feasible. Phase 3 clinical trials of ibrutinib and idelalisib are ongoing.

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Mantle Cell Lymphoma: The Changing Landscape

Andre Goy, MD

Mantle cell lymphoma is an aggressive, biologically heterogeneous lymphoma subtype that is typically associated with a poor prognosis. Outcomes for patients with MCL have been improving, with the median overall survival almost doubling in the past 30 years.[1] The introduction of intensive treatment approaches, particularly regimens containing high-dose Ara-C, has led to durable progression-free survival. Alternative strategies under evaluation involve novel agents and new combinations, and the use of maintenance therapy.

Current Approaches in Younger Patients

There have been few randomized trials comparing therapies in MCL. An analysis from the prospective National Comprehensive Cancer Network (NCCN) NHL database found a significant improvement in PFS and OS with aggressive regimens (rituximab, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [R-HCVAD]; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] plus R-HCVAD; or R-HCVAD plus high-dose therapy/autologous stem cell transplant [HDT/ASCT]) versus standard R-CHOP.[2]

The Nordic MCL2 trial reported significant efficacy with an intensive frontline induction therapy including rituximab, Ara-C, and HDT/ASCT, with a 5-year EFS rate of 63%.[3] Longer follow-up after a median of 6.5 years confirmed the durability of responses, with median OS and response duration exceeding 10 years (Figure 7).[3] Other trials evaluating Ara-C–containing induction regimens have reported similar efficacy outcomes, with 5-year EFS rates of 56% to 65%.[4,5]

The randomized MCL Younger trial, which compared 2 induction regimens in patients ages 65 or younger with previously untreated MCL, reported a significant improvement in efficacy with alternating courses of CHOP and dihydroxyacetone phosphate (DHAP) plus rituximab followed by a high-dose Ara-C–containing myeloablative regimen and ASCT versus R-CHOP alone followed by myeloablative radiochemotherapy. The median time to treatment failure was 88 months and 46 months, respectively (P=.038), with a median remission duration after ASCT of 84 and 49 months, respectively (P=.0001).[6] At the final analysis, the median overall survival was not reached in the Ara-C–containing arm versus 82 months in the R-CHOP arm (P =.045). The efficacy improvement observed in the intensive therapy

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arm versus the R-CHOP arm was attributed to higher rates of CR (55% vs 40%; *P*=.0028) and molecular CR (83% vs 51%; *P*<.0001), as post-transplant response rates were similar between arms.[6]

However, even these intensive therapies are associated with the development of relapse and chemoresistance, and late relapses have been observed more than 5 years after the completion of therapy.[3]

Current Approaches for Older Patients

Approximately half of patients with MCL are not candidates for intensive approaches owing to older age. Alternative regimens have been evaluated for these patients in an attempt to balance efficacy with toxicity. A multicenter phase 2 pilot study evaluated a modified R-HCVAD regimen that lacked methotrexate or cytarabine, followed by rituximab maintenance therapy, as initial treatment in 22 patients with MCL.[7] The regimen was effective, yielding an ORR of 77% (64% CR); after a median follow-up of 37 months, the median PFS was 37 months and the median OS was not reached.

A subsequent trial evaluated the same modified R-HCVAD regimen with the addition of bortezomib and an extension of maintenance rituximab beyond 2 years in 30 patients with MCL (median age, 61 years).[8] This regimen was associated with an ORR of 90% (77% CR) and 3-year PFS and OS rates of 63% and 86%, respectively. The larger cooperative group trial E1405 evaluated modified R-HCVAD plus bortezomib in 75 patients with previously untreated MCL (median age, 62 years), and allowed for HDT/ASCT or maintenance rituximab after induction therapy.[9] The ORR was 97% (68% CR), and the median PFS was 4 years. There was no significant difference in outcomes with maintenance rituximab versus ASCT.

Another strategy that has been evaluated in MCL is the combination of bendamustine and rituximab. In an open-label, multicenter, randomized, phase 3 noninferiority trial, bendamustine and rituximab was significantly more effective than R-CHOP in patients with MCL, with a median PFS of 35.4 months and 22.1 months, respectively (*P*=.0044). There was no significant difference in OS.[10] Bendamustine and rituximab was also better tolerated than R-CHOP. Most recently, the phase 3 BRIGHT (Bendamustine Rituximab Investigational Non-Hodgkin's Trial) study reported a higher CR rate with bendamustine and rituximab versus R-CHOP or R-CVP in patients with MCL (50% vs 27%).[11] The ongoing STiL (Study Group Indolent Lymphomas) trial is comparing bendamustine and rituximab followed by observation or maintenance rituximab for 2 years in patients who are not eligible for ASCT.

In 2012, Kluin-Nelemans and colleagues reported results from a randomized, controlled trial comparing treatment strategies in 532 older patients with MCL (median age, 70 years).[12] Patients were assigned to 8 cycles of rituximab, fludarabine, and cyclophosphamide or R-CHOP; responding patients were then randomly assigned to maintenance rituximab or interferon alfa. Although CR rates were similar with rituximab, fludarabine, and cyclophosphamide and R-CHOP (40% and 34%, respectively), the rate of progressive disease was higher with rituximab, fludarabine, and cyclophosphamide versus R-CHOP (14% vs 5%), resulting in a significantly lower 4-year OS rate (47% vs 62%; *P*=.005). Among patients assigned to maintenance therapy, rituximab was significantly more effective than interferon, with 4-year PFS rates of 58% and 29%, respectively (*P*=.01). Among patients with a response to R-CHOP, maintenance rituximab was associated with a significant improvement in OS versus maintenance interferon, with 4-year OS rates of 87% and 63%, respectively (*P*=.005).

In summary, recent clinical trials in older patients with MCL indicate that R-CHOP alone is inadequate, whereas bendamustine plus rituximab offers a new backbone against which novel agents may be evaluated. Maintenance approaches will likely become a routine aspect of MCL management. Given the high rates of relapse and treatment failures, alternative approaches are needed.

New Approaches With Existing Agents

In recent years, several novel agents have been introduced in an attempt to improve outcomes for patients with relapsed MCL. Multiple trials have demonstrated the activity of single-agent bortezomib in patients with MCL, with response rates up to 45%.[13-16] In 2006, bortezomib was FDA-approved for the treatment of patients with MCL who have received at least 1 prior therapy.

Bortezomib has also been evaluated as a component of combination therapy. There is some evidence that the addition of bortezomib to R-CHOP or to dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone, and rituximab (EPOCH-R) may increase the response rate and extend PFS beyond that observed in earlier studies in previously untreated patients[17-19] and in patients with relapsed/refractory MCL.[20] A phase 3 trial comparing bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) versus R-CHOP in patients with newly diagnosed MCL was recently completed, and results of this trial are highly anticipated.[21]

The mTOR inhibitor temsirolimus has also been evaluated in MCL, demonstrating single-agent response rates of approximately 40%.[22,23] Lowering the temsirolimus dose to 25 mg/week from 250 mg/week reduced the rate of grade 3/4 hematologic toxicity (54% vs 84%) but yielded a similar response rate.[22,23] In a phase 2 study in

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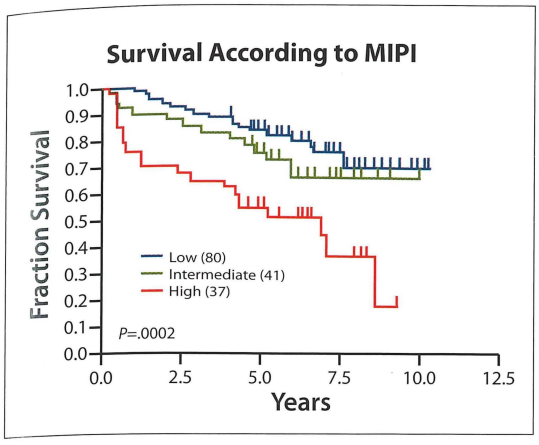


Figure 7. The Nordic MCL2 trial reported significant efficacy with an intensive frontline induction therapy including rituximab, Ara-C, and HDT/ASCT in younger patients with mantle cell lymphoma. ASCT, autologous stem cell transplant; HDT, high-dose therapy; MIPI, Mantle Cell International Prognostic Index. Adapted from Geisler CH, et al. *Br J Haematol.* 2012;158:355-362.[3]

69 assessable patients with relapsed or refractory MCL, the combination of temsirolimus and rituximab was associated with an ORR of 59% (19% CR) in the overall population, 63% in rituximab-sensitive patients, and 52% in rituximab-refractory patients.[24] Ongoing phase 1/2 trials are evaluating other temsirolimus-containing combinations, including rituximab and cladribine,[25] bendamustine and rituximab,[26] bendamustine plus rituximab, and idelalisib.

The immunomodulatory agent lenalidomide has also demonstrated activity in MCL, with single-agent response rates of 35% to 50% in patients with relapsed or refractory MCL. In the registrational EMERGE (A Study to Determine the Efficacy and Safety of Lenalidomide in Patients With Mantle Cell NHL Who Have Relapsed or Progressed After Treatment With Bortezomib or Are Refractory to Bortezomib) trial, 134 patients with relapsed/refractory MCL received single-agent lenalidomide until progression or unacceptable toxicity.[27] All patients had failed therapy with anthracyclines, cyclophosphamide, rituximab, and bortezomib. In this heavily pretreated population (median of 4 prior regimens), lenalidomide was associated with an ORR of 28% (8% CR/CRu) and a median response duration of 16.6 months. Response rates were similar across patient subgroups with the exception of patients with high levels of lactate dehydrogenase.

Based on the outcomes in the EMERGE trial, lenalidomide received FDA approval for use in MCL in patients with relapse or progression after 2 prior therapies, including bortezomib. The most common grade 3/4 adverse events were neutropenia (43%), thrombocytopenia (28%), and anemia (11%). Although this trial was not randomized, these outcomes appear superior to chemotherapy in this setting.

A pooled analysis of 206 patients with relapsed/refractory MCL enrolled in multiple clinical trials confirmed the activity of single-agent lenalidomide, yielding an ORR of 32% (10% CR/CRu).[28] Clinical trials are ongoing to further assess the role of lenalidomide in MCL; the phase 2 SPRINT (A Study to Determine the Efficacy of Lenalidomide Versus Investigator's Choice in Patients With Relapsed or Refractory Mantle Cell Lymphoma [MCL]) trial comparing lenalidomide versus investigator's choice in patients with relapsed or refractory MCL was recently completed,[29] and phase III trials are evaluating the role of lenalidomide in the initial treatment of MCL.

Combinations of lenalidomide with other newer agents have also been reported in phase 1/2 trials. In patients with relapsed/refractory MCL, lenalidomide plus rituximab was associated with an ORR of 57% (36% CR) and a median response duration of 18 months, although there was significant myelotoxicity.[30] A combination of rituximab, lenalidomide, and bortezomib in the first-line or second-line treatment of MCL was associated with an ORR of 82% (32% CR), and a lenalidomide dose of 10 mg/day was selected for further study in that combination, based on toxicity with higher doses.[31]

Novel Agents in MCL

Multiple emerging agents are being evaluated in MCL, including several that target different aspects of the BCR pathway. In a phase 1/2 trial, the SYK inhibitor fostamatinib showed modest single-agent activity in MCL; 200-mg twice daily dosing was selected for further evaluation based on toxicity with higher doses.[32]

The PI3Kδ inhibitor idelalisib has been evaluated in MCL. The phase 1 study of idelalisib included 40 patients with relapsed or refractory MCL who had received a median of 4 prior treatments.[33] Across dosing groups, idelalisib was associated with an ORR of 40% (67% among patients receiving at least 150 mg twice daily), although the responses were often transient, with a median duration of 3 months. The most common grade 3 or higher adverse events included ALT/AST elevations (20%), diarrhea (17%), and pneumonia (12%). In vitro studies have revealed higher levels of the PI3K isoform p110α in relapsed MCL, suggesting that inhibition of both p110α and PI3Kδ could be a more effective strategy in MCL therapy.[34]

The BTK inhibitor ibrutinib has also been evaluated in MCL. After a phase 1 study suggested antitumor activ-

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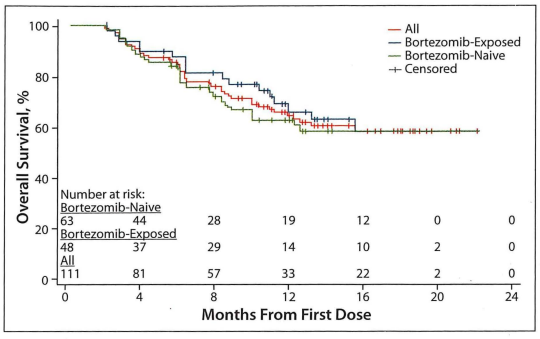


Figure 8. Overall survival in a phase 2 trial evaluating ibrutinib in patients with relapsed or refractory mantle cell lymphoma. Adapted from Wang ML et al. *N Engl J Med.* 2013.[35]

ity of ibrutinib in MCL, a phase 2 trial was undertaken evaluating oral ibrutinib administered at 560 mg daily in 111 patients with relapsed or refractory MCL who had received a median of 3 prior therapies.[35] The most frequent treatment-related adverse events were mild or moderate diarrhea, fatigue, and nausea; grade 3/4 adverse events were infrequent, aside from neutropenia (16%), thrombocytopenia (11%), and anemia (10%). Ibrutinib was associated with an ORR of 68% (21% CR); responses were observed regardless of prior bortezomib treatment. The median duration of response was 18 months, median PFS was 14 months, and median OS was not reached (Figure 8). The response rate appeared to improve over time, even beyond 12 months.

The Bcl-2–specific BH3 mimetic ABT-199 is being evaluated in a phase 1 dose-escalation study in patients with relapsed NHL. Interim results suggest substantial antitumor activity with ABT-199 in MCL, with 7 of 7 enrolled patients attaining a partial response.[36] The agent appeared to be well tolerated, with no dose-limiting toxicity, no tumor lysis syndrome in patients with MCL, and no evidence of dose-dependent thrombocytopenia. The only grade 3/4 adverse event reported in more than 2 patients was anemia (10%).

In summary, the treatment landscape in MCL is changing dramatically, with the introduction of new active combinations in the frontline setting, including options for patients ineligible for transplant; the use of maintenance therapy to improve outcomes; and a wide array of targeted agents under evaluation in relapsed and refractory patients. Clinicians should encourage patients to enroll in clinical trials to help expedite the evaluation of these new therapies.

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