Novel Agents for Follicular Lymphoma

John P. Leonard[1] and Peter Martin[1]

[1]Center for Lymphoma and Myeloma, and Division of Hematology and Medical Oncology, Weill Cornell Medical College and New York Presbyterian Hospital, New York, NY

Unlabeled and radiolabeled anti-CD20 monoclonal antibodies have had a significant impact in the care of patients with follicular lymphoma (FL) over the past decade. More recently, bendamustine has demonstrated activity in refractory FL, and has been explored as initial therapy and in novel combinations. Whereas outcomes for this patient population have significantly improved, there remains substantial unmet need for patients who require more effective and better-tolerated therapies. Novel anti-CD20 antibodies and other immunotherapies against different B-cell antigens are under active investigation. The proteosome inhibitor bortezomib and the immunomodulatory agent lenalidomide have demonstrated single-agent activity and are currently in randomized trials. Other novel compounds have demonstrated activity in broad-based clinical studies in B-cell malignancies. However, considerable challenges remain in efficiently demonstrating which patient subsets can benefit from these novel compounds and which combinations may have the greatest clinical benefit in further improving outcomes for patients with FL.

There are three great ironies in the current development of novel therapies for patients with follicular lymphoma (FL). First, more successful frontline approaches have made the assessment of new agents as part of initial therapy a more difficult and long-term endeavor. Second, patients with resistant disease need new agents. However, the demonstration of efficacy in this patient population can be difficult. Third, in some cases, the more targeted a drug—and the more rational the design—the more challenging it may be to establish single-agent activity. Indeed, to a large extent, this is the situation we currently face. The anti-CD20 monoclonal antibody rituximab has become part of the standard of care for nearly all patients with FL and has been associated with significant improvements in overall survival. The radioimmunotherapy agents yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab have substantial activity, and are well tolerated. The chemotherapeutic agent bendamustine was recently approved by the US Food and Drug Administration (FDA) for treatment of patients with rituximab refractory indolent lymphoma and is positioned to become a component of frontline therapy. In the current environment, it is remarkable that, through clinical trials, FL patients have access to more novel drugs than ever.

Targeted agents can be broadly classified into three groups: (1) those that target the surface of the cell (eg, monoclonal antibodies), (2) those that are directed against intracellular processes (eg, proteasome inhibitors), and (3) those that target the cancer microenvironment (eg, immunomodulatory drugs).

Agents That Target the Cell Surface

Most therapeutic monoclonal antibodies are designed to target glycoproteins on the surface of cancer cells. From the cell surface, the antibody is able to interact with other components of the immune system, resulting in antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), the putative dominant mechanisms of action of rituximab. Despite taking place at the cell surface, the effects of antibody binding may extend to the intracellular domain, where alterations in cell signaling can induce cell apoptosis. Monoclonal antibodies may also have effects beyond the cancer cell itself, resulting in a "vaccinal effect." The choice of antigen, the properties of the antibody (ie, the degree and site of binding, the ability to interact with the immune system or alter signal transduction), and the decision to coadminister additional drugs all may enhance efficacy in certain settings.

Novel Anti-CD20 Antibodies

Several novel antibodies under preclinical and clinical assessments incorporate structural modifications that are hoped to deliver clinical advantages, in comparison with rituximab. Antibody binding to effector cells through activating Fc receptors (FcγRIII) is requisite for ADCC and has therefore been central to new antibody development. The importance of CDC and direct cytotoxicity in elimination of cancer cells have been debated, but have also been the focus of novel antibody design. Finally, engineering away from murine or chimeric protein structures toward humanized or fully human antibodies has resulted in decreased immunogenicity, changes in pharmacokinetics, and, most importantly, potential enhancement of therapeutic effects.

The fully human, anti-CD20 ofatumumab was engineered to target an epitope more proximal to the surface of B cells and to have a slower off-rate than rituximab.[1,2] Classified as a type I antibody, ofatumumab is able to induce translocation of CD20 into detergent-insoluble lipid rafts.[1] As a result, ofatumumab is able to induce significantly greater CDC than rituximab at lower target-antigen concentrations.[1] Additionally, the Fc portion of ofatumumab binds more strongly with FcγRIII and appears to produce greater ADCC than rituximab in vitro.[3] Ofatumumab was recently approved by the FDA for treatment of patients with chronic lymphocytic leukemia (CLL) that is refractory to fludarabine and alemtuzumab, a patient population that is poorly responsive to rituximab. A phase I/II study in patients with previously treated FL evaluated four weekly infusions at doses from 300 to 1000 mg.[4] Toxicity was similar to that of rituximab, and clinical response rates ranged from 20% to 62%, depending on the cohort. The median time to progression was 8.8 months. To assess whether a novel anti-CD20 might overcome resistance to rituximab, ofatumumab was assessed with eight weekly infusions at one of two dose levels (500 or 1000 mg) in 116 rituximab refractory patients with FL.[5] Those subjects who received

the higher dose demonstrated an overall response rate (ORR) of 10%, including one complete response (CR). Given the refractory nature of this population (median four prior regimens) one could argue that comparisons of ofatumumab to rituximab might be better suited for a less resistant patient population. Ongoing studies include those employing ofatumumab in combination with chemotherapy (NCT00494780).

Veltuzumab (hA20) is a humanized IgG1 with identical anti-CD20 complementarity-determining regions such as rituximab.[6] Preclinical studies demonstrated activity similar to that of rituximab, although with a slower off-rate and enhanced CDC in several B-cell lymphoma cell lines.[6] In a multicenter phase I/II study, no grade 3 or grade 4 toxicity was observed, and 44% of patients with previously treated FL achieved an objective response (27% CR rate) with intravenous doses of 80 to 750 mg/m^2 weekly for 4 weeks.[7] Preliminary results of a phase I/II study of subcutaneously injected veltuzumab have been reported, with doses ranging from 80 to 320 mg/m^2 every 2 weeks for four doses.[8] Tolerability and bioavailability were good. Of 15 patients, including 12 with FL, there were eight responders, including three CRs. It is noteworthy that veltuzumab has been associated with responses in patients treated with very low doses administered either intravenously or subcutaneously.

GA101 is a humanized antibody generated from Chinese hamster ovary cells that have been engineered to produce antibodies with afucosylated Fc region carbohydrates. The result is an antibody that binds more strongly to FcγRIII and has improved ADCC.[9] As a type II antibody, GA101 lacks the ability to induce CDC, but appears to be better at direct induction of cell death than type I antibodies.[9] Data from two phase I clinical trials have been reported. In the first trial, 21 subjects, including 13 with FL, were treated with nine doses of GA101 ranging from 50 to 2000 mg.[10] No dose-limiting toxicity was observed, and side effects consisted primarily of grade 1/2 infusion reactions. Five CRs/unconfirmed CRs (CRu) and four partial responses (PRs) were demonstrated. In the second trial, 22 patients (10 with FL) received four weekly doses (100 to 2000 mg), followed by maintenance therapy of one dose every 3 months for up to 2 years.[11] Half of all patients were refractory to prior rituximab. Five PRs were observed, and toxicity was similar to the first trial.

AME-133 is a human IgG1 antibody with high affinity for CD20 and an Fc region capable of binding to FcγRIII with significantly greater affinity than rituximab.[12] Preclinical studies suggested that AME-133 was more effective than rituximab at natural killer cell activation and could overcome the effects of less favorable FcγRIII polymorphisms.[13] A phase I/II trial in patients with relapsed FL (nonrituximab refractory) and at least one allele corresponding to the low affinity FcγRIII is ongoing.

Antibodies Against Targets Other Than CD20

A target antigen should be preferentially expressed on malignant cells, stably expressed on the cell surface, and mediate an important cellular function. The fact that CD20 may not completely fulfill these criteria, yet is remarkably effective as an antibody target, demonstrates that a nonideal antigen can still be valuable.

CD22 is widely expressed on normal and malignant B cells, and it plays a role in the mediation of B-cell activation and adhesion. Unlike CD20, CD22 constitutively internalizes and is degraded without recycling. Epratuzumab is a humanized IgG1 anti-CD22 antibody associated with both ADCC and direct cytotoxicity in preclinical studies.[14] Phase I/II studies demonstrated significant objective response rates across various dose levels in both FL and diffuse, large B-cell lymphoma (DLBCL).[15,16] Toxicity consisted primarily of infusion-related reactions. Concurrent administration of epratuzumab and rituximab was evaluated in two studies.[17,18] Objective responses were noted in about two-thirds of patients with FL and about half of a smaller number of DLBCL subjects, including some CRs. An ongoing study of the Cancer and Leukemia Group B (CALGB) is evaluating the combination of epratuzumab + rituximab in the initial treatment for FL (NCT00553501).

CD37 is expressed at high concentrations on the surface of B cells and mature B-cell lymphomas. TRU-016 is a small, modular immunopharmaceutical comprised of a IgG1 variable regions (VL and VH) and a small, engineered constant region.[19] The small size of the SMIP theoretically allows for improved tumor penetration relative to larger monoclonal antibodies. Preclinical testing demonstrated the activity of TRU-016 alone and in combination with other cytotoxic agents in B-cell lymphoma cell lines.[20] A phase I trial of TRU-016 in patients with CLL is underway with trials in FL likely to follow (NCT00614042).[21]

Milatuzumab is a humanized antibody against CD74. Although the precise role of CD74 is unclear, it appears to function both in antigen presentation, as the invariant chain of class II MHC, and as an accessory-signaling molecule in B-cell differentiation.[22–24] Unlike CD20, CD74 is present on the cell surface for a very brief period of time (~ 10 minutes) before it is endocytosed. Preclinical data demonstrated that milatuzumab was active in vitro and in vivo against B-cell lymphomas and that the mechanism of action was distinct from that of rituximab.[25] We are conducting a phase I trial in patients with previously treated B-cell lymphomas (NCT00504972). CD74 may serve as an ideal target for immunoconjugates or combinations with other antibodies that rely on ADCC or CDC.

Galiximab is a chimeric human primate anti-CD80 antibody with single-agent activity and excellent tolerability in previously treated FL.[26] Based on promising preclinical data, a phase I/II trial was conducted with the combination of galiximab + rituximab in patients with previously treated FL.[27] An ORR of 66% and a 12.1-month median progression-free survival (PFS) were observed. The CALGB subsequently evaluated the combination as initial treatment in FL using four weekly doses of both agents, followed by an "extended induction" of both agents administered once every 2 months for an additional four doses each.[28] The ORR was 70%, including a 44% CR/CRu rate. The response rate correlated with the Follicular Lymphoma International Prognostic Index (FLIPI) score, with 75% of patients with a low-risk FLIPI obtaining a CR. This regimen is an example of the potential for combination biologic therapy as an initial approach to FL, which may allow for a less toxic regimen that is sufficiently effective to delay the need for a chemotherapy-containing regimen. Despite the apparent activity of the combination in patients with low-risk FLIPI scores, development of galiximab appears to be on hold, a result of the challenges of drug development in the new era.

Antibodies that target two antigens are termed "bispecific." Blinatumomab is an anti-CD3/anti-CD19 bispecific antibody that engages T cells and malignant B cells. Phase I studies have demonstrated tolerability and clinical activity in B-cell lymphoma.[29] Antibody 22–20 is a hexavalent bispecific antibody composed of epratuzumab conjugated with four Fab regions from veltuzumab.[30] The agent is a potent inducer of ADCC and direct cytotoxicity, but not CDC, despite an ability to translocate the target antigens into lipid rafts.

Further clinical evaluation will be required to determine if this new class of antibodies is as successful as preclinical testing might suggest.

Immunoconjugates in FL

The use of a radionuclide or a toxin conjugated to a B-cell specific monoclonal antibody allows for another mechanism to induce cell killing beyond the direct antibody and immune effects. Unlike naked antibodies, which appear to exert their effects largely from the cell surface, conjugated antibodies often benefit from internalization. Inotuzumab ozogamicin (CMC-544) is a humanized anti-CD22 antibody conjugated to calicheamicin. In a phase I study, toxicity included thrombocytopenia, asthenia, nausea, and neutropenia. The ORR for all patients treated at all doses was 39%; in FL, 68% of patients responded at the maximum tolerated dose. A follow-up study enrolled 110 patients treated with the combination of CMC-544 and rituximab.[31] For 38 patients with recurrent FL, the ORR was 87%, with a median PFS of 23.6 months. Further studies of this drug as a single agent or in combination are ongoing (NCT00868608, NCT0155496).

SAR3419 is an antibody-drug conjugate comprised of a humanized anti-CD19 IgG1 antibody to the tubulin inhibitor DM4, a maytansinoid derivative. A phase I study was conducted in 29 subjects (12 with FL), and used an infusion every 3 weeks, with doses ranging from 10 to 270 mg/m^2/dose.[32] Dose-limiting toxicity consisted of blurred vision due to corneal changes. Notably, hematologic toxicity was not a significant issue with this regimen. Five objective responses were observed. An additional study evaluating other dosing schedules is currently ongoing (NCT00796731).

The anti-CD22 antibody epratuzumab conjugated with ^{90}Y-DOTA was studied in a phase I trial of fractionated radioimmunotherapy.[33] Patients received two or three weekly doses of study drug, with increasing doses of ^{90}Y. The highest total dose received was 45 mCi/m^2 (15 mCi/m^2 $\times$ 3), significantly higher than the maximum dose of ^{90}Y-ibritumomab tiuxetan (a flat dose of 32 mCi). Of the 34 patients with previously treated FL, 74% responded with 62% obtaining a CR/CRu. There was a significant relationship between radiation dose and response rate. We are conducting a phase I/II study of fractionated ^{90}Y-epratuzumab in combination with veltuzumab in patients with untreated follicular lymphoma (NCT01147393).

Agents That Target Intracellular Processes

Intracellular processes relevant to FL include signaling through the B-cell receptor and the PI3K-AKT-mTOR pathway. The development of agents that target these pathways is covered in another article in this section by Drs. Witzig and Gupta. Other relevant targets include bcl-6, the mdm2-p53 axis, the Bcl-2 family, and the ubiquitin-proteasome pathway.

Proteosome Inhibitors

The proteasome plays a vital role in the regulation of several cell mechanisms important to lymphoma, including the cell cycle (via the cyclins, the cyclin-depending kinases (cdk), and the cdk inhibitors), tumor suppression (via p53), and gene transcription (via NF-κB [nuclear factor-κ light-chain enhancer of activated B cells]).[34] The precise mechanism by which proteasome inhibition induces cell death is unclear and may be related to a variety of these pathways, depending on the setting, highlighting the fact that more than drugs with one mechanism of action may have advantages over those that target a single tyrosine kinase.

Bortezomib is a small molecule inhibitor of the proteosome approved in the United States for the treatment of multiple myeloma and mantle cell lymphoma. Bortezomib has been evaluated in a number of phase II studies in patients with FL.[35–37] Interestingly, the median time to response to bortezomib in FL appears longer than in other B-cell malignancies, the significance of which is unclear.[38] DeVos and colleagues[39] evaluated the combination of bortezomib with rituximab in a phase II study that enrolled subjects with previously treated FL or marginal zone lymphoma not refractory to prior rituximab. In arm A, patients received bortezomib 1.3 mg/m^2 twice weekly for 2weeks in each 3-week cycle + rituximab 375 mg/m^2 weekly for the first 4 weeks only (N = 41), whereas in arm B, patients received bortezomib 1.6 mg/m^2 weekly for 4 weeks in each 5-week cycle + rituximab 375 mg/m^2 weekly for the first 4 weeks only (N = 40). The response rates and time to progression were similar (49% vs 43% and 7 months vs 10 months in arm A vs arm B, respectively), whereas the weekly regimen appeared slightly better tolerated. A phase II randomized trial of rituximab alone or in combination with bortezomib is ongoing. The National Cancer Institute of Canada recently reported preliminary results from a phase II trial in which bortezomib 1.3 mg/m^2 on days 1 and 8 was added to standard rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) in patients with advanced-stage FL.[40] Six of 95 patients reported grade 3 neurotoxicity, with no grade 4 events. The overall response and CR rates were 84.6% and 47%, respectively. In a similar phase I trial, two different schedules of bortezomib were substituted for vincristine in R-CVP in patients with previously treated indolent or mantle cell lymphoma.[41] Two of four patients treated with twice weekly bortezomib experienced grade 3/4 neurotoxicity. The ORR was 64% in the twice-weekly group, suggesting that targeted agents have the potential to replace traditional cytotoxic chemotherapeutic agents as components of some regimens.

The novel proteasome inhibitor MLN9708 has demonstrated activity in preclinical lymphoma models and is currently undergoing evaluation in a phase I trial in patients with relapsed lymphoma.[42] MLN9708 also exists in oral form and is undergoing evaluation in multiple myeloma. Carfilzomib is a novel proteasome inhibitor with significant activity in multiple myeloma and no reported evidence of neurotoxicity. Two phase I studies have been conducted in patients with relapsed hematologic malignancies. Further experience in FL will be required to determine its activity and safety profile.[43,44]

Bcl-2 Inhibitors

The Bcl-2 family is a group of proteins that share at least one of four Bcl homology domains (BH1-BH4). Family members may be either proapoptotic (eg, Bax, Bak) or antiapoptotic (eg, Bcl- X_L, Bcl-2), depending on the domains expressed. The 14;18 translocation, which occurs in the vast majority of FL, results in juxtaposition of the *BCL2* gene next to the immunoglobulin heavy chain gene, resulting in constitutive expression. At least three Bcl-2 inhibitors are currently in development in B-cell malignancies. Apogossypol is an orally active analog of gossypol. The negative enantiomer of gossypol, AT-101, demonstrated some activity in patients with CLL, but was associated with dose-limiting hepatotoxicity and gastrointestinal toxicity.[45] A subsequent two-stage phase II trial of AT-101 + rituximab in patients with FL did not meet the threshold to proceed to stage II, perhaps related to limitations in the dose.[46] In preclinical testing, apogossypol was less toxic than gossypol and had greater activity.[47] Clinical testing will be required to validate the preclinical results. ABT-263 is an orally available, small molecule BH3 mimetic that primarily inhibits Bcl-X_L. In a phase I/II study,

patients with previously treated lymphoid malignancies were treated with cycles of either 14 days of ABT-263 followed by 1 week off or 21 days of continuous ABT-263.[48] Thrombocytopenia was common due to the expression of Bcl-X_L in megakaryocytes, but appeared to be better with continuous dosing over intermittent dosing. Activity was seen primarily in CLL, suggesting that combination with other agents may be required for maximal effect in other lymphomas. Obatoclax is novel BH3 mimetic that appears to sensitize rituximab-resistant cells to treatment with bortezomib.[49] The combination has undergone phase I testing in patients with mantle cell lymphoma and is currently undergoing additional clinical evaluation in combination with multiple other agents.[50]

mdm2 Inhibitors

Dysfunction of the p53 tumor suppressor has been implicated in multiple cancers. The human homolog of murine double-minute protein 2 (mdm2) is a natural inhibitor of p53 and is frequently upregulated in FL. Nutlin-3 is a novel small molecule antagonist of mdm2 with preclinical activity in mantle cell lymphoma.[51] This drug and other small molecule mdm2 inhibitors are most likely to demonstrate activity in those patients with unmutated TP53 genes, offering a potential pretreatment predictor of response.

Bcl-6 Inhibitors

The bcl-6 protein is a transcriptional repressor expressed in germinal center B cells. Translocations involving the *BCL6* gene are common in FL and appear to be a harbinger of high-grade transformation.[52] Hsp90 stabilizes bcl-6, allowing it to have a greater effect on target genes. The hsp90 inhibitor PU-H71 has demonstrated preclinical activity in bcl-6–dependent large-cell lymphomas, making it potentially relevant for clinical development in B-cell malignancies derived from the germinal center, including FL.[53]

Agents That Target the Microenvironment

Lenalidomide

The immunomodulatory agent lenalidomide is approved for the treatment of patients with myeloma and myelodysplastic syndromes. The precise mechanism of action of lenalidomide remains unclear, but likely involves multiple effects on the tumor microenvironment, including downregulation of tumor necrosis factor-α, interleukin-6, interleukin-8, vascular endothelial growth factor, and activation of T and NK cells.[54,55] Several studies have demonstrated the utility of this novel agent in non-Hodgkin lymphoma, including FL. In an international phase II study, patients with previously treated indolent lymphoma received lenalidomide 25 mg once daily on days 1 to 21 of every 28-day cycle.[56] The ORR was 23% (27% in FL), with a median PFS of 4.4 months. The most common grade 3/4 events were neutropenia and thrombocytopenia. Based on preclinical data that the activation of NK cells by lenalidomide may improve rituximab-induced ADCC, several groups have undertaken studies of the combination. Sixteen patients with relapsed indolent lymphoma received lenalidomide, initially as described previously, but subsequently lowered to 20 mg due to tumor lysis, plus four weekly doses of rituximab beginning on day 15 of cycle 1 and repeated for four additional doses the patient had less than a CR after cycle 2.[57] In addition to two patients with grade 3 tumor lysis, fatigue (12%), neutropenia (18%), and hyponatremia (18%) were the most common grade 3/4 adverse events. Twelve patients responded, including five patients with a CR/CRu. An ongoing phase II study, under the auspices of the CALGB, randomizes patients to lenalidomide alone or in combination with rituximab (NCT00238238). Patients are required to have relapsed disease following rituximab therapy, but must not be rituximab resistant. The primary objectives are overall response and time-to-disease progression, with one aim to determine whether rituximab augments the effects of lenalidomide. In an approach that could change the management of patients with newly diagnosed, low FLIPI-risk FL, Fowler and colleagues[58] tested lenalidomide 20 mg on days 1 to 21 + rituximab on day 1 for up to six cycles in patients with untreated indolent lymphoma. Preliminary results in 19 patients demonstrated an ORR of 86%, with a 75% CR/CRu rate. Longer follow-up with a larger number of patients will be required to determine whether this approach is worth carrying forward to a phase III study.

Targeting T-Regulatory Cells

Another approach to targeting the tumor microenvironment in FL involves interference with T-regulatory (T-regs) cells in tumor masses that may interfere with the host immune response against the tumor. Denileukin diftitox is an immunotoxin directed against the CD25 antigen expressed on T-regs. Ongoing studies are assessing the combination of denileukin diftitox in combination with rituximab, with the hope that depletion fo T-regs will enhance the antilymphoma effects of the anti-CD20 antibody (NCT00460109).

Conclusions

Therapeutic monoclonal antibodies have provided significant benefit for patients with FL. Essentially all patients with B-cell lymphoma receive rituximab at multiple times over their treatment. Novel anti-CD20 agents offer the potential for enhanced activity relative to that of rituximab, although clinical data have not been compelling to date. Agents directed against different targets offer the possibility of combination with rituximab or significant activity on their own. Many challenges exist in determining the optimal use of novel agents. New anti-CD20 antibodies will require randomized comparative trials or demonstration of effectiveness in rituximab refractory patients (elusive thus far). Novel combinations also require vetting through comparative studies with rituximab alone. Whether or not such combinations are effective, and warrant the associated costs, remains to be seen.

The broad array of novel agents, heterogeneous clinical behavior, and range of standard therapies presents difficulties in development of novel agents for FL. One way to overcome these challenges may be to explore the use of new agents as part of initial therapy, where the disease may be somewhat more uniform in its characteristics and where the variables of prior therapy are eliminated. The CALGB has been exploring novel combinations of biologic agents (without chemotherapy) as initial treatment for FL.

Despite the challenges, the promise of novel therapeutic agents in FL suggests the possibility that better tolerated and more effective treatments are on the horizon to help clinicians and researchers continue to improve outcomes for patients.

Disclosures

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Off-label drug use: Off-label and investigational lymphoma therapies.

Correspondence

John P. Leonard, MD, Clinical Director, Center for Lymphoma and Myeloma, and Professor, Division of Hematology and Medical Oncology, Weill Cornell Medical College and New York Presbyterian Hospital, 525 East 68th St., Box 403, New York, NY 10065; Phone: (646) 962-2068; Fax: (646) 962-1605; e-mail: jpleonar@med.cornell.edu

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