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## Augmenting Clinical Responses through Intracellular Pathways in B-cell Malignancies

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# Treating Newly Diagnosed CLL: Benefits and Risks of the “Watch and Wait” Approach and Novel Treatment Options

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The decision to initiate treatment in patients with early chronic lymphocytic leukemia (CLL) is complex and involves multiple factors. In general, the revised criteria for initiating treatment include advanced-stage disease (Binet stage C or Rai stage III-IV disease) or early-stage active disease, defined as progressive anemia or thrombocytopenia; progressive, symptomatic, or massive splenomegaly or lymphadenopathy; progressive lymphocytosis with an increase of greater than 50% within 2 months or lymphocyte doubling time of less than 6 months; refractory autoimmune anemia or thrombocytopenia; and constitutional symptoms such as weight loss, fatigue, fever, and night sweats.<sup>1</sup>

The primary goal of treatment for patients with newly diagnosed CLL is complete eradication of disease with low toxicity and improved quality of life. Patient-related factors, such as age, comorbidities, and disease characteristics, can negatively influence treatment outcomes. Other factors that may influence the treatment decision include the availability of approved drugs, clinical trials, and cost.

Potential advantages of treating early-stage disease include a low disease burden, which may be more sensitive to treatment, thus resulting in improved quality of life and prolonged progression-free survival (PFS). The possibility of eradicating minimal or residual disease

is theoretically higher, and thus early treatment may prevent the development of resistant clones. Potential disadvantages of early treatment include cost and the risk of toxicities, including infectious complications, cytopenias, and possibly carcinogenesis.

The more recently defined poor-risk features of CLL include unmutated immunoglobulin heavy-chain variable-region (IgV<sub>H</sub>), zeta-chain-associated protein kinase of 70 kDa (ZAP-70) overexpression, elevated CD38 expression, and deletions in 17p and 11p.<sup>2-5</sup> A landmark study by Döhner and colleagues showed that genomic aberrations are independently associated with shorter survival.<sup>6</sup> In a large, retrospective analysis of patients with CLL/small lymphocytic lymphoma, 5 variables independently predicted shorter survival: 17p or 6q deletion; age of at least 60 years; beta2-microglobulin at least 2 mg/L; albumin <3.5 g/dL; and creatinine at least 1.6 mg/dL.<sup>7</sup> A follow-up analysis of a subset of these patients showed that patients with genomic abnormalities or ZAP 70-positive disease received treatment earlier than patients without those risk factors.

To evaluate the benefit of treatment in patients with early-stage high-risk CLL, Bergmann and colleagues conducted a randomized phase III trial of fludarabine versus observation in patients with high-risk CLL.<sup>8</sup> Compared

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with observation, fludarabine was associated with significantly longer median PFS in the 188 evaluable patients (24.2 vs 15.9 months;  $P=.03$ ), though there was no difference in overall survival.

Ongoing clinical trials continue to evaluate the benefit of various treatment regimens for improving outcomes in patients with early-stage high-risk CLL. An individualized approach including novel therapeutic agents and established treatments may improve clinical outcomes in patients with CLL.

### Bendamustine in CLL

The nitrogen mustard derivative bendamustine, which is a bifunctional molecule with an alkylating agent and an antimetabolite, has demonstrated significant efficacy in CLL. Bendamustine has multiple mechanisms of action, including DNA-damage stress response and induction of mitotic catastrophe, an apoptotic form of cell death that occurs during the metaphase. In 1975, Anger and colleagues reported that bendamustine was more effective than cyclophosphamide in 70 patients with untreated CLL, with response rates of 82% and 32%, respectively.<sup>9</sup> From 2001 to 2006, relatively small phase I/II clinical trials of bendamustine—almost all in patients with previously treated CLL—confirmed the agent's activity, reporting overall response rates (ORR) of 56–94%, with 7–30% complete responses (CR).<sup>10–13</sup>

Combination therapy with bendamustine plus rituximab has demonstrated significant activity in patients with relapsed CLL, with an ORR of 77% (15% CR) in a phase II study.<sup>14</sup> In 2009, the German CLL Study Group (GCLLSG) presented results of a phase II study of bendamustine plus rituximab in patients with previously untreated CLL.<sup>15</sup> In 110 evaluable patients, the ORR was 91%, including 33% CR. Of 7 patients with 17p deletion, 3 responded to treatment. The combination also induced minimal residual disease negativity in the blood in 58% of patients and in the bone marrow in 28%. The GCLLSG is conducting a randomized phase III trial of bendamustine plus rituximab versus fludarabine plus cyclophosphamide and rituximab (FCR) in patients with previously untreated CLL.

The phase II Velcade, Rituximab, Treanda in Combination for Relapsed Lymphoma (VERTICAL) study evaluated the combination of bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma. The regimen was associated with CR and partial response rates of 47% and 37%, respectively, for an ORR of 84%.<sup>16</sup> Treatment-related serious adverse events were reported in 27% of patients, including 5% with febrile neutropenia.

### Ofatumumab in CLL

The human anti-CD20 monoclonal antibody ofatumumab has demonstrated significant antileukemic activity and was recently approved for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. Ofatumumab is associated with an ORR of 58%, median PFS of 5.7 months, and median overall survival of 13.7 months in these patients.<sup>17</sup> In 79 patients with bulky tumor masses refractory to fludarabine, the ORR was 47%, median PFS was 5.9 months, and median overall survival was 15.4 months.

A randomized, multicenter, phase II trial evaluated 2 doses of ofatumumab plus fludarabine and cyclophosphamide in 61 patients with previously untreated CLL.<sup>18</sup> The CR rate was higher with ofatumumab 1,000 mg versus 500 mg (50% vs 32%), though the ORR was similar between arms (73% and 77%, respectively). The most commonly reported grade 3/4 adverse event was infection in 11 patients, with 6 patients developing febrile neutropenia. Ongoing studies are evaluating 1,000-mg ofatumumab in combination with chemotherapy.

### Lenalidomide in CLL

Single-agent lenalidomide induces an ORR of 32–47% in patients with relapsed or refractory CLL.<sup>19–20</sup> A phase II study evaluated the combination of lenalidomide and rituximab in 60 patients with relapsed CLL. In 44 evaluable patients, the ORR was 64%. The most common grade 3/4 treatment-related adverse events were neutropenia (43%), fatigue (27%), and fever of unknown origin (18%).<sup>21</sup>

### Other Combination Regimens in CLL

Studies evaluating various combination regimens were presented at ASH 2009. One regimen demonstrating significant activity in CLL was cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR). Among 59 evaluable patients with previously untreated CLL, CR, nodular partial response, and partial response rates were 70%, 3%, and 18%, respectively, for an ORR of 92%.<sup>22</sup> The regimen also appeared active in patients with 17p deletion, with a CR rate of 57% and an ORR of 78%, though the median time-to-progression was 18 months. Major infections were reported in 15% of patients, and cytomegalovirus reactivation occurred in 12% of patients, all of whom were receiving valacyclovir prophylaxis. There was 1 death due to cytomegalovirus pneumonia.

The GCLLSG presented results of a multicenter phase II trial of fludarabine, cyclophosphamide, and

alemtuzumab in patients with relapsed or genetic high-risk CLL.<sup>23</sup> In 52 patients evaluable for response, the ORR was 68%, with 22% CR. Responses were independent of fluorescence in situ hybridization (FISH) status.

The Cancer and Leukemia Group B (CALGB) Study 10101 evaluated alemtuzumab consolidation therapy after fludarabine and rituximab induction in 58 patients with CLL.<sup>24</sup> The addition of alemtuzumab was associated with an increase in CR rate from 29% to 66%, with 42% of patients attaining minimal residual disease negativity. However, alemtuzumab added no overall survival or PSF benefit. Moreover, it was associated with significant infectious toxicity; 6 patients died from infection while in remission, both during alemtuzumab therapy and for up to 7 months after therapy. Thus, while alemtuzumab was associated with improvements after fludarabine plus rituximab induction, the risk of serious infections, particularly in patients attaining remission with induction therapy, emphasizes the need for risk-adapted therapy in CLL.

Early clinical trials with selected novel agents were also presented at ASH 2009. Agents demonstrating preliminary activity in CLL included novel anti-CD20 antibodies, a small-molecule Bcl-2 inhibitor, an anti-CD37 agent, and a PI3-kinase inhibitor.<sup>25-29</sup>

Also at ASH 2009, the GCLLSG presented results of a randomized phase III trial showing that the addition of rituximab (R) to fludarabine and cyclophosphamide (FC) improves overall survival in treatment-naïve patients with CD20-positive CLL.<sup>30</sup> At 38 months, the proportion of patients alive was significantly higher with FCR versus FC (84% vs 79%;  $P=.01$ ). FCR was also associated with a higher CR rate (44% vs 22%;  $P<.001$ ) and a longer median PFS (52 vs 38 months;  $P<.001$ ; hazard ratio, 0.56; 95% CI, 0.46–0.69).

In summary, based on existing data, younger patients with good performance status and no comorbidities appear to benefit from a combination regimen of a purine analog and rituximab, such as FCR. Older patients with comorbidities may benefit from less cytotoxic treatments and clinical trials with targeted agents. The approval of bendamustine for CLL is especially relevant for older patients and for those with comorbidities that render FCR suboptimal therapy. Patients with p53 deletions may benefit from alemtuzumab-containing therapies such as CFAR, but caution is needed in prevention of opportunistic infections. CLL associated with 11p deletion appears to respond to FCR or FC.

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# The Impact of Rituximab on Treatment Paradigms for B-cell Lymphomas

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Outcomes in patients with follicular lymphoma, the most frequently occurring indolent lymphoma subtype, have improved dramatically in recent years. Follicular lymphoma can now be considered a chronic disease, with median overall survival now exceeding 18 years.<sup>1-2</sup> This improvement is due largely to the introduction of the anti-CD20 monoclonal antibody rituximab.

Multiple randomized clinical trials have demonstrated a significant survival benefit with the addition of rituximab to first-line chemotherapy in patients with follicular lymphoma and diffuse large B-cell lymphoma (DLBCL). Maintenance rituximab has also been associated with prolonged PFS after chemotherapy and after rituximab or rituximab plus chemotherapy in patients with follicular lymphoma.

There are a number of unresolved issues regarding the optimal use of rituximab in non-Hodgkin lymphoma (NHL). For follicular lymphoma, these include the optimal schedule, dose, and duration of rituximab maintenance. For DLBCL, current questions include the role of maintenance rituximab after induction therapy with chemotherapy plus rituximab, and the role of dose-dense rituximab. For all patients, an important goal is to define biologic factors associated with rituximab sensitivity and resistance.

## Optimizing Rituximab Use

Multiple maintenance schedules have been evaluated in patients with follicular lymphoma. The European Organisation for Research and Treatment of Cancer (EORTC) regimen of 375 mg/m<sup>2</sup> once every 3 months may be considered most effective, as it maintains significant antibody levels.<sup>3</sup> However, some advocate different schedules, and the issue remains unresolved.

In DLBCL, a phase II study showed that dose-dense rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is feasible in patients supported by pegfilgrastim.<sup>4</sup> DENSE-R-CHOP-14 is now being evaluated in a phase III study comparing dose-dense R-CHOP with conventional R-CHOP in DLBCL. In a 2006 randomized trial by Habermann and colleagues,<sup>5</sup> rituximab administered as induction or maintenance therapy with CHOP chemotherapy significantly prolonged failure-free survival in older DLBCL patients. After R-CHOP, however, there was no benefit associated with maintenance rituximab. The important question of rituximab maintenance in DLBCL is also being addressed by the ongoing NHL-13 trial, in which patients receiving R-CHOP induction therapy are randomized to rituximab maintenance versus observation.

**Table 1.** CD20 Type I and Type II Antibodies

Type I Monoclonal Antibodies	Type II Monoclonal Antibodies
Localize CD20 to lipid rafts	Do not localize CD20 to lipid rafts
High complement-dependent cytotoxicity	Low complement-dependent cytotoxicity
Antibody-dependent cellular cytotoxicity activity	Antibody-dependent cellular cytotoxicity activity
Full number of binding sites/B-cell	Half number of binding sites/B-cell
Weak homotypic aggregation	Strong homotypic aggregation
Weak direct cell death induction	Strong direct cell death induction
Rituximab Ofatumumab Veltuzumab Ocrelizumab AME-133 PRO131921	GA101 B1 (tositumomab)

Several groups are actively exploring biologic prognostic markers in DLBCL. An international consortium is evaluating the expression of markers in hundreds of clinical trial samples, with the goal of developing a biologic International Prognostic Index (IPI) in DLBCL.

### Rituximab Exposure and Resistance

Current clinical trial data support the use of rituximab in multiple settings during the first years of therapy for follicular lymphoma. First-line treatment includes rituximab plus chemotherapy followed by rituximab maintenance every 2 months for up to 2 years. At first relapse, treatment can include rituximab plus chemotherapy for 6–8 cycles followed by rituximab maintenance every 3 months for up to 2 years. At subsequent relapses, patients may again receive rituximab in combination with chemotherapy or another agent. Overall, patients are heavily exposed to rituximab during the first 5 years of treatment.

The question of rituximab resistance is an important one. Not all patients respond to rituximab, either alone or in combination with chemotherapy. Some patients develop progressive disease during rituximab-containing therapy, and others relapse or progress early after rituximab-therapy. The U.S. Food and Drug Administration defines rituximab resistance as having stable disease on, or progression during, rituximab monotherapy or rituximab plus chemotherapy, or developing progressive disease or relapse within 6 months after the last rituximab or rituximab/chemotherapy treatment.

In the phase II Groupe d'Etude des Lymphomes de l'Adulte (GELA) study of patients with follicular NHL, rituximab monotherapy was associated with a significant ORR of 73%, though 27% of patients did not respond,

indicating that the disease was refractory to rituximab in the first-line setting. Trials evaluating rituximab maintenance have shown that 20% of patients develop progression or relapse within 15 months and 30% develop progression or relapse within 2.5 years.<sup>6-7</sup> Based on these findings, an estimated 70% of patients become refractory to rituximab during first-line and second-line therapy for follicular lymphoma.

### Role of Novel Monoclonal Antibodies

Alternative treatments are clearly needed for patients with rituximab-resistant disease. Many novel monoclonal antibodies are currently being evaluated; in order for such an agent to be considered superior to rituximab, it would need to demonstrate one of the following qualities: activity in rituximab-refractory patients; superiority to rituximab in head-to-head randomized clinical trials in rituximab-naïve patients; equal efficacy and less toxicity compared with rituximab; or equal efficacy and toxicity but lower cost than rituximab.

Anti-CD20 monoclonal antibodies currently being evaluated include both type I and type II antibodies, which differ substantially in their characteristics and functions (Table 1). Type I antibodies under investigation include ofatumumab, veltuzumab, ocrelizumab, AME-133, and PRO131921; type II antibodies include GA101 and B1 (tositumomab).

Ofatumumab is a fully human monoclonal antibody that demonstrated activity in a phase I/II study in patients with relapsed/refractory follicular lymphoma.<sup>8</sup> A subsequent phase II study of single-agent ofatumumab showed limited activity in patients refractory to rituximab plus chemotherapy and greater activity in patients refractory to rituximab monotherapy.<sup>9</sup>

Veltuzumab is a fully humanized second-generation anti-CD20 antibody that has shown activity in several trials, including a multicenter phase I/II study in patients with refractory/recurrent NHL.<sup>10</sup> GA101 is the first humanized and glycoengineered type II anti-CD20 monoclonal antibody to be evaluated in clinical trials. In a phase I study, GA101 demonstrated activity in patients with relapsed/refractory CD20-positive NHL.<sup>11</sup>

Novel anti-CD20 monoclonal antibodies have demonstrated the same favorable toxicity profiles as rituximab. In general, pharmacodynamic parameters do not correlate with response, and no clear dose-effect relationships have been detected. They are associated with significant efficacy, although response rates in rituximab-refractory patients are modest. It will be important to compare these agents against a rituximab plus chemotherapy regimen to evaluate the additional role of these promising new antibodies.

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# Novel Targeted Agents and Monoclonal Antibodies for Aggressive B-cell Lymphoma

Myron S. Czuczman, MD

Various new therapeutic approaches are being evaluated to improve the treatment of aggressive B-cell lymphoma. Targeted therapy has several potential advantages, including less nonspecific toxicity compared with chemotherapy; the potential of targeting resistance pathways to reduce or reverse chemoresistance; non-cross-resistant mechanisms of action; and additive or synergistic activity in combination with monoclonal antibodies or other drugs.

Targeted therapies being evaluated in B-cell lymphomas include antibodies directed against surface proteins, proteasome inhibitors, immunomodulatory drugs, histone deacetylase inhibitors, and inhibitors of various signaling pathways.

## Agents Targeting Surface Antigens

B cells express many surface antigens that could serve as targets for monoclonal antibody therapy. Epratuzumab is a humanized monoclonal antibody directed against the CD22 determinate RFB4. Binding of epratuzumab to the CD22 ligand results in rapid internalization of the CD22/antibody complex. The agent may block binding of natural ligands and elicit signals similar to natural ligands, leading to inhibition of the B-cell receptor. Epratuzumab has demonstrated activity in recurrent/refractory DLBCL alone and in combination with rituximab.<sup>1-2</sup> The agent has demonstrated no significant toxicity in current clinical trials of more than 400 patients. In 2009, Micallef

and colleagues presented the final results of the North Central Cancer Treatment Group trial N0489, a multicenter phase II study of epratuzumab and rituximab in combination with CHOP (ER-CHOP) in 78 patients with previously untreated DLBCL.<sup>3</sup> The regimen was associated with an ORR of 95%, with CR/unconfirmed complete response (CRu) rates of 74% and 72%, respectively, in patients with low-risk and high-risk IPI. Overall survival, PFS, and event-free survival rates were 89%, 87%, and 79%, respectively, at 1 year, and 79%, 79%, and 69% at 2 years. These outcomes compare favorably to prior R-CHOP studies, and ER-CHOP appears to offer an improvement over R-CHOP in patients with higher-risk disease. A randomized phase III trial would be needed to directly compare ER-CHOP versus R-CHOP.

Another monoclonal antibody being evaluated in DLBCL is the humanized anti-CD40 agent dacetuzumab. In a multicenter phase II open-label study in 38 patients with relapsed DLBCL, dacetuzumab monotherapy was associated with a 10% ORR; there was no correlation between response and CD40 expression, DLBCL subtype, or Fc $\gamma$ RIIIa polymorphisms.<sup>4</sup>

### Proteasome Inhibition

The proteasome inhibitor bortezomib blocks the proteolytic action of the proteasome. By blocking degradation of I- $\kappa$ B, bortezomib inhibits nuclear factor- $\kappa$ B (NF- $\kappa$ B), leading to upregulation of pro-apoptotic proteins, imbalance in cell-cycle regulatory proteins, and decreased expression of essential proteins related to angiogenesis and cell adhesion. NF- $\kappa$ B target genes have been shown to be highly expressed in activated B-cell-like (ABC) DLBCL, lending further support to NF- $\kappa$ B inhibition using bortezomib as a therapeutic strategy.<sup>5</sup>

In a phase II trial, single-agent bortezomib had no activity in recurrent DLBCL.<sup>6</sup> Combination therapy with bortezomib plus chemotherapy was active in the ABC subtype, with a response rate of 83% versus 13% in patients with germinal-center DLBCL ( $P < .002$ ). Median overall survival was also significantly longer in ABC versus germinal center DLBCL (10.8 vs 3.4 months;  $P = .003$ ). These findings suggest that different treatments may be appropriate in genetically distinct DLBCL subtypes, with NF- $\kappa$ B inhibition via bortezomib showing activity in ABC DLBCL. The identification of biomarkers that can predict the success or failure of salvage agents will be a valuable tool in selecting treatment in the future.

### Lenalidomide

The immunomodulatory thalidomide analog lenalidomide is also demonstrating efficacy in aggressive NHL.

In the NHL-003 study, which included 108 patients with relapsed/refractory DLBCL, single-agent lenalidomide was associated with an ORR of 35% and a median PFS of 3.5 months.<sup>7</sup> An oral agent, lenalidomide can be administered as outpatient therapy but is associated with myelosuppression that often leads to dose reduction. In NHL-003, 41% of patients developed grade 3/4 neutropenia and 44% had dose reductions or interruptions due to adverse events.

### mTOR Inhibition

Mammalian target of rapamycin (mTOR) is a serine-threonine kinase component of the PI3-kinase/Akt signaling pathway. Signaling through the mTOR pathway plays a role in translational control, modulation of apoptosis, cell cycle regulation, metabolic modulation, and neuronal function. These functions reveal mTOR inhibition as an attractive target for cancer therapy.<sup>8</sup>

Two mTOR inhibitors have demonstrated promising activity in B-cell lymphoma. In a phase III trial of 162 evaluable patients with heavily pretreated mantle cell lymphoma (MCL), temsirolimus at 175 mg 3 times weekly followed by 75 mg weekly was associated with significant improvement over standard therapies as assessed by ORR (22% vs 2%;  $P = .0019$ ) and median PFS (4.8 vs 1.9 months;  $P = .0009$ ).<sup>9</sup> In a phase II trial of 37 patients with aggressive NHL, single-agent everolimus was associated with an ORR of 32%, including 35% in DLBCL and 29% in MCL.<sup>10</sup>

### CD22-Targeted Immunoconjugate

CMC-544 (inotuzumab ozogamicin) is an immunoconjugate of an IgG4 anti-CD22 monoclonal antibody covalently linked to CalicheDMH, a potent DNA-binding cytotoxic antitumor antibiotic.<sup>11</sup> IgG4 humanized antibodies have no biologic activity, but instead function as a vehicle. In this case, the antibody binds to CD22, causing internalization of the antibody/ligand complex, along with the conjugated chemotherapeutic component. Combination therapy with CMC-544 and rituximab demonstrated improved antitumor activity against NHL in preclinical models.<sup>12</sup>

In 2008, Fayad and colleagues presented preliminary results of a phase I/II study evaluating the clinical activity of CMC-544 plus rituximab in patients with refractory aggressive NHL.<sup>13</sup> Prior rituximab treatment was required, though rituximab-refractory patients were excluded. At the maximum tolerated dose, the regimen was associated with an ORR of 71% in patients with DLBCL ( $n = 14$ ), including 43% CR, and an ORR of 88%, including 44% CR, in patients with follicular lymphoma ( $n = 16$ ).

## Syk-Targeted Therapy

One role of B-cell receptor (BCR) signaling is activation of the spleen tyrosine kinase (Syk) pathway, leading to amplification of the BCR signal. BCRs also transduce low-level tonic survival signals independent of receptor engagement. Inhibition of Syk-dependent tonic BCR signaling through a Syk inhibitor selectively targets tonic BCR signaling and lymphoma cell survival.<sup>14</sup> The oral Syk inhibitor fostamatinib disodium is a potent pro-drug of R406. In a phase I/II trial, fostamatinib disodium was associated with a 21% ORR in 23 patients with DLBCL and was associated with reversible toxicities.<sup>15</sup>

Gene expression profiling has revealed protein kinase C-beta as a rational therapeutic target in DLBCL. The protein kinase C-beta inhibitor enzastaurin was evaluated in a phase II trial of 55 patients with recurrent DLBCL.<sup>16</sup> After 56 days, 22% of patients were free from progression and 6% attained CR. Several other studies of enzastaurin in aggressive NHL are ongoing, both in the induction and maintenance settings.

## Other Novel Therapeutic Approaches

Deacetylases (DACs) are enzymes that regulate gene transcription and other cellular processes essential to tumor growth; cell motility, invasion, proliferation, and survival; and angiogenesis. DAC inhibitors can reactivate genes that had been epigenetically silenced, such as tumor suppressor genes. DAC inhibition also induces cell death in tumor cells, but not in normal cells.

Bcl-2 antagonists are also being developed that promote cell death by antagonizing anti-apoptotic proteins. These BH3 mimetics bind to anti-apoptotic proteins such as MCL1 or Bcl-2, leading to downstream effects that induce apoptosis. Tumor cells that overexpress anti-apoptotic proteins can be resensitized with these types of agents.

In summary, a variety of novel targeted agents are demonstrating promising activity in NHL. In the future, therapy for aggressive lymphoma will likely involve the use of risk analysis to individualize treatment. Ongoing translational research will identify additional novel targets and predictors of response. Combinations of targeted agents will likely increase direct anti-tumor activity while decreasing nonspecific toxicities.

With the growing number of targeted therapies being developed, it will be important to evaluate the logical use of these agents, whether in sequence or in combination

with other agents, and in the maintenance setting. Moreover, longitudinal long-term follow-up of patients will be critical to understand the role of different agents. With these continuing advances, a higher cure rate in aggressive NHL is an achievable goal within our lifetime.

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# Indolent B-cell Lymphoma: New Therapeutic Developments

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**A**lthough outcomes have improved dramatically in patients with indolent B-cell lymphomas, no treatments are curative; effective therapies are needed with each relapse. Types of novel agents demonstrating promising activity include chemotherapeutic agents, monoclonal antibodies, agents targeting signaling pathways, immunomodulatory agents, and apoptosis-inducing agents.

## Bendamustine

Bendamustine was evaluated in 2 multicenter phase II studies in patients with relapsed follicular and low-grade rituximab-refractory lymphoma. In 176 evaluable patients, single-agent bendamustine was associated with an ORR of 76%, including 23% CR/CRu.<sup>1</sup> Responses were similar across Follicular Lymphoma International Prognostic Index (FLIPI) categories. This response rate is the highest reported to date with a single agent in this refractory population.

After Rummel and colleagues demonstrated the activity of bendamustine plus rituximab in relapsed indolent NHL,<sup>2</sup> they conducted the randomized, multicenter, open-label phase III Study Group Indolent Lymphomas (STIL) trial comparing bendamustine/rituximab versus R-CHOP in previously untreated indolent lymphoma. In 513 evaluable patients, bendamustine/rituximab was superior to R-CHOP in regard to median PFS (55 vs 35 months;  $P=.00012$ ) and CR rate (40% vs 30%;  $P=.026$ ).<sup>3</sup> Bendamustine/rituximab was also associated with fewer toxicities, including less grade 3/4 neutropenia (11% vs 47%;  $P<.0001$ ) and leukocytopenia (12% vs 38%;  $P<.0001$ ), fewer infectious complications ( $P=.0025$ ), less paresthesias ( $P<.001$ ), and less alopecia ( $P<.001$ ). These findings challenge the standard of R-CHOP for the initial treatment of patients with follicular lymphoma and MCL.

## Monoclonal Antibodies

Multiple monoclonal antibodies targeting various proteins have been evaluated in indolent B-cell malignancies. These include anti-CD20 antibodies, including ofatu-

mumab, veltuzumab, and GA101, as well as antibodies targeting other proteins. The anti-CD20 antibodies have demonstrated similar activity, and it is not yet clear which agents would be most appropriate in different settings.

## Galiximab

The anti-CD80 monoclonal antibody galiximab has been evaluated as monotherapy and in combination with rituximab. The phase II CALGB 50402 trial evaluated galiximab plus rituximab in 61 patients with previously untreated follicular lymphoma. ORR and CR rates ranged from 92% and 75%, respectively, in patients with low FLIPI scores to 55% and 27% in patients with high FLIPI scores.<sup>4</sup>

## Antibody-Like Constructs

Blinatumomab is a bispecific antibody construct that engages cytotoxic T-cells. In a phase I study in patients with relapsed NHL, blinatumomab was associated with a 100% ORR at the highest dose evaluated, though there was significant toxicity at this dose.<sup>5</sup>

Tru16 is a small modular immuno-pharmaceutical (SMIP), which is a single-chain polypeptide that dimerizes in solution. SMIPs offer antibody-like target specificity and binding but have a smaller size designed to enhance biodistribution. Tru16 is directed against CD37, a molecule present on all CLL and most lymphomas. Tru16 has more potent antibody-dependent cellular cytotoxic activity than rituximab, and induces rapid B-cell depletion in CLL/NHL. Ongoing research is investigating the potential clinical use of Tru16 in lymphoma.

## Other Investigational Approaches

Several small-molecule inhibitors are also being evaluated in indolent NHL. The Syk inhibitor fostamatinib, which showed activity in recurrent DLBCL in a phase I/II trial, also appears to have some activity in recurrent follicular lymphoma.<sup>6</sup> The PI3 kinase pathway is also being targeted using CAL-101, a potent oral inhibitor of

the PI3-kinase p110 $\Delta$ . In a phase I study, CAL-101 was associated with a 56% response rate in relapsed/refractory B-cell malignancies.<sup>7</sup>

Lenalidomide has demonstrated efficacy in a range of B-cell malignancies. A phase II trial of single-agent lenalidomide in relapsed/refractory indolent NHL demonstrated an ORR of 23%, with durable responses.<sup>8</sup> Lenalidomide is also active in relapsed/refractory MCL, demonstrating an ORR of 43%.<sup>9</sup> Fowler and colleagues recently presented results of a phase II study evaluating lenalidomide plus rituximab as initial treatment of follicular lymphoma.<sup>10</sup> Among the 13 patients evaluable for response, the ORR was 85%, with 77% CR.

Multiple apoptosis-targeted therapies are also being explored in NHL, including agents that target the cell-intrinsic pathway and the cell-extrinsic pathway. Examples include the anti-survivin suppressant YM155 and ABT-263, which inhibits Bcl-2 family proteins.

In conclusion, many targeted therapies are currently being investigated in NHL, including at least 3 proteasome inhibitors, at least 3 mTOR inhibitors, 6 PI3-kinase inhibitors, at least 15 histone deacetylases (HDAC) inhibitors, and many anti-CD20 agents. It will be important to evaluate preclinical and early clinical data to determine the most promising agents. Single-agent activity is desirable but not essential, as agents may have synergistic activity. As new agents are developed, enrollment in clinical trials will be essential to adequately evaluate these new approaches.

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# Targeting the Critical Pathways in Mantle Cell Lymphoma and Multiple Myeloma

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**M**antle cell lymphoma and multiple myeloma (MM) are relatively rare hematologic malignancies that have historically been associated with poor outcomes. There is significant overlap between MCL and MM in their biology and active agents. The last 20 years have brought significant improvements in therapy for MM, with the approval of bortezomib, thalidomide, and lenalidomide. Ongoing studies with combinations of biologic agents are showing unprecedented response rates in the frontline setting, and numerous targeted agents are currently being evaluated for patients upon relapse.

MCL is rare, accounting for approximately 6% of NHL. In the past 30 years, survival has almost doubled from 2.7 years to 4.8 years, likely due to multiple factors.<sup>1</sup> Frontline therapy for MCL is controversial, as there is no standard or consensus therapy. While dose-intensive approaches followed by transplantation are improving PFS, their effect on overall survival is uncertain, and novel treatment options are clearly needed.

## Targeting Cell Cycle Progression

MCL is primarily driven by cyclin D1 and cell cycle deregulation, making cell cycle progression an attractive therapeutic target. Cyclins are known to form complexes with cyclin-dependent kinases (CDK); these complexes tightly regulate cell cycle progression. Thus, multiple CDK inhibitors have been developed that prevent the formation of cyclin-CDK complexes. After initial trials with CDK inhibitors showed inadequate inhibition of the target, a more intense treatment regimen was developed that requires tumor lysis syndrome prophylaxis that must be scheduled in the intensive care unit. Second-generation CDK inhibitors have demonstrated preliminary activity in multiple hematologic malignancies, including MCL, and clinical trials are ongoing.

## Targeting the Proteasome

Proteasome inhibition has demonstrated significant activity in NHL. Although protein degradation was thought to be nonspecific, it is now understood to be a highly regulated process essential for cell cycle control and to prevent

the intracellular accumulation of abnormal proteins. The phase II PINNACLE trial evaluated single-agent bortezomib in 155 patients with relapsed or refractory MCL. In 141 evaluable patients, bortezomib was associated with an ORR of 32%, including 8% CR/CRu, with a median duration of response of 9.2 months.<sup>2-3</sup> Responses were observed in heavily pretreated patients, including those receiving prior high-intensity treatment.

Despite these findings, single-agent bortezomib is not a recommended treatment for MCL. Evidence suggests that bortezomib is additive or synergistic with many cytotoxic and/or biologic agents; recent and ongoing studies are evaluating the safety and efficacy of bortezomib in various settings added to rituximab; R-CHOP; rituximab, etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide (R-EPOCH); dose-intense therapy; Bcl-2 inhibitors; CDK inhibitors; and lenalidomide.

Second-generation proteasome inhibitors, including carfilzomib and salinosporamide A, may enhance proteasome inhibition while minimizing toxicity.<sup>4-5</sup> Next steps for proteasome inhibition include the development of ligase-specific inhibitors, agents that specifically target ubiquitinated proteins, and immunoproteasome inhibitors.

## Targeting Intracellular Signaling Pathways

The mTOR pathway is central to the activity of multiple receptor tyrosine kinases, and integrates multiple oncogenic pathways to allow the continued growth and proliferation of tumor cells. In a phase II trial in 35 patients with relapsed MCL, single-agent temsirolimus 250 mg weekly was associated with an ORR of 38%, though 91% of patients developed grade 3/4 adverse events.<sup>6</sup> A 10-fold lower dose of 25 mg weekly was found to be equally effective, with a 41% ORR, but with a better toxicity profile.<sup>7</sup>

An international, randomized phase III trial compared 2 doses of temsirolimus versus a single-agent investigator choice in 162 patients with relapsed/refractory MCL. Compared with investigator choice, higher-dose temsirolimus was associated with a significantly higher ORR (22% vs 2%;  $P=.0019$ ) and longer median PFS (4.8

vs 1.9 months;  $P=.0009$ ).<sup>8</sup> Recent and ongoing trials are evaluating temsirolimus in combination with rituximab in relapsed MCL and in combination with rituximab and cladribine in frontline MCL. Additional mTOR inhibitors, including everolimus and deforolimus, are also being evaluated in aggressive NHL.<sup>9-11</sup>

Apoptosis modulators are also being evaluated, including agents targeting the Bcl-2 pathway. Initial findings with Bcl-2 inhibitors were disappointing, though multiple pan-Bcl-2 inhibitors, including obatoclax and ABT-263, are showing strong activity in small lymphocytic lymphoma/CLL.<sup>12-13</sup>

## HDAC Inhibitors

HDACs regulate transcription epigenetically by modulating chromatin status, thus inducing or repressing transcription. Multiple classes of HDAC inhibitors have been developed with different selectivity. Preclinical activity showed induction of differentiation, cell cycle arrest, and apoptosis with these agents, as well as synergy with various other compounds. Ongoing combinations with bortezomib and vorinostat are being evaluated in MM and MCL.

## Anti-angiogenic Therapy

Neoangiogenesis is an essential part of tumor progression. Antiangiogenic agents have been developed that interfere with the interactions between tumor cells and endothelial cells through different mechanisms. These include targeting the vascular endothelial growth factor (VEGF, bevacizumab, aflibercept), targeting the VEGF receptor (tyrosine kinase inhibitors), inhibiting hypoxia inducing factor (HIF1) (small-molecule inhibitors), disrupting endothelial cell function (thalidomide, lenalidomide), and inhibiting endothelial cell propagation (angiostatin, endostatin).

## Lenalidomide

In several trials, lenalidomide has been shown to be effective in patients with MCL.<sup>14-16</sup> Lenalidomide has very impressive activity and a long duration of response. Ongoing trials are evaluating lenalidomide in bortezomib-refractory MCL (EMERGE trial), lenalidomide versus

investigator choice in relapsed/refractory MCL (SPRINT trial), lenalidomide as maintenance therapy after first-line chemotherapy (RENEW trial), and combinations of lenalidomide with other biologics.

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# The Best Combination Regimens for Newly Diagnosed Multiple Myeloma

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**N**ovel biologically based treatments are being developed for MM, which target the MM cells themselves as well as the bone marrow micro-environment. In recent years, 4 new drugs have been approved for the treatment of MM: thalidomide, bortezomib, lenalidomide, and doxorubicin HCl liposome injection (in combination with bortezomib). Studies are continuing to evaluate the optimal use of these agents in different treatment settings.

The randomized, double-blind Southwest Oncology Group (SWOG) trial S0232 demonstrated the superiority of lenalidomide plus high-dose dexamethasone over high-dose dexamethasone alone in newly diagnosed MM.<sup>1</sup> In 133 patients evaluable for response, lenalidomide/dexamethasone was more effective than dexamethasone in regard to estimated 1-year PFS (77% vs 55%;  $P=.002$ ), ORR (85% vs 51%;  $P=.001$ ), and CR rate (22% vs 4%).

The randomized, multicenter, phase III E4A03 trial compared 2 doses of dexamethasone in combination with lenalidomide in previously untreated MM. Compared with high-dose dexamethasone, low-dose dexamethasone was associated with a significant reduction in nonhematologic toxicity, thromboembolic events, infections, and early death.<sup>2</sup> Low-dose dexamethasone was also associated with a significant improvement in overall survival at 12 months. PFS was also borderline positive for low-dose dexamethasone versus high-dose dexamethasone. Low-dose dexamethasone is now the preferred regimen to use in combination with lenalidomide in first-line MM. However, response rates were significantly higher with high-dose versus low-dose dexamethasone (79% vs 68%;  $P=.008$ ). Patients receiving more than 4 cycles of lenalidomide plus low-dose dexamethasone had a higher ORR of 91%, including 22% CR. Longer follow-up is needed to fully evaluate the efficacy of this regimen.

## Bortezomib

The proteasome inhibitor bortezomib has also been evaluated in combination with dexamethasone in induction therapy for MM. The randomized phase III Inter-groupe Francophone du Myelome (IFM) 2005/01 study

compared bortezomib/dexamethasone versus standard vincristine, doxorubicin, dexamethasone (VAD) as induction therapy prior to autologous stem cell transplantation (ASCT) in 482 patients with previously untreated MM. Compared with VAD, bortezomib/dexamethasone was associated with significantly higher response rates both after induction therapy and after ASCT.<sup>3</sup> Bortezomib/dexamethasone was also associated with a significant PFS benefit. This was the first trial to demonstrate that better induction responses lead to better outcomes after ASCT.

The next regimen to be evaluated was a 3-drug combination of bortezomib, thalidomide, and dexamethasone (VTD), which was compared against thalidomide/dexamethasone (TD) in a randomized, multicenter, phase III trial in 460 patients with newly diagnosed MM. VTD was significantly more effective than TD as assessed by responses to induction and post-ASCT responses (Table 2).<sup>4</sup> At a follow-up of 15 months, 2-year PFS rates were also higher with VTD versus TD (90% vs 80%;  $P=.009$ ).

Neurotoxicity can be a consequence of both bortezomib and thalidomide; however, lenalidomide is not associated with neuropathy. Therefore, Richardson and colleagues undertook a clinical trial to replace thalidomide with lenalidomide in the 3-drug regimen.<sup>5</sup> In 65 patients with newly diagnosed MM who received bortezomib, lenalidomide, and dexamethasone, the ORR was 100%, including 26% CR and 74% very good partial response. The regimen was well tolerated. Another study is evaluating the addition of cyclophosphamide to this regimen, though it would be difficult to improve upon a 100% response rate. Other regimens and schedules are being evaluated to decrease treatment-associated neuropathy. Moreover, randomized phase II trials are currently underway to directly compare various first-line regimens.

## Regimens for Nontransplant Candidates

Combination regimens containing melphalan are also being evaluated in MM; these should not be administered to patients eligible for transplantation, as melphalan may affect stem cells. One such regimen is VMP (bortezomib,

**Table 2.** VTD Versus TD: Clinical Outcome

Response to Induction			
Response*	Induction		
	VTD (n=226)	TD (n=234)	P Value
CR/nCR	32%	12%	<.001
≥VGPR	62%	29%	<.001
≥PR	94%	79%	<.001

Post-ASCT Response			
Response	First SCT		
	VTD (n=226)	TD (n=234)	P Value
CR	43%	23%	<.001
CR/nCR	55%	32%	<.001
≥VGPR	76%	58%	<.001

\*Modified European Group for Blood and Marrow Transplantation criteria.

ASCT=autologous stem cell transplantation; CR=complete response; nCR=near complete response; PR=partial response; SCT=stem cell transplantation; TD=thalidomide/dexamethasone; VGPR=very good partial response; VTD=bortezomib, thalidomide, and dexamethasone.

Data from Cavo M et al.<sup>4</sup>

melphalan, and prednisone), which was evaluated in the randomized, international phase III Velcade as Initial Standard Therapy in Multiple Myeloma (VISTA) trial in patients with symptomatic MM ineligible for transplantation. A total of 682 patients received melphalan plus prednisone with or without bortezomib. Compared with MP, VMP was associated with a higher ORR (71% vs 35%;  $P<.001$ ), higher CR rate (30% vs 4%;  $P<.001$ ), longer median time-to-progression (24.0 vs 16.6 months;  $P<.000001$ ), and higher 3-year overall survival rate (72% vs 59%;  $P=.0032$ ).<sup>6</sup> VMP was also effective in patients with poor prognostic characteristics, suggesting that the addition of a novel agent to melphalan/prednisone may overcome poor-risk features in MM.

A randomized phase III trial evaluated the addition of thalidomide to VMP in 511 patients ineligible for transplantation. The proportion of patients attaining at least very good partial response was significantly higher

with VMPT versus VMP (55% vs 45%;  $P<.001$ ), though there was also a substantial increase in sensory neuropathy. Reducing the frequency of bortezomib from twice weekly to once weekly lowered the risk of neuropathy without sacrificing efficacy.<sup>7</sup> In general, recent phase III clinical trials evaluating new combinations are demonstrating overall survival rates at least as good as those attained with ASCT.

In considering initial therapy, physicians should first ensure that patients do not have smoldering stage I MM, which would not require immediate treatment. For patients requiring treatment, the therapeutic approach should be based on whether the patient is a candidate for transplantation. The initial regimen is selected based on patient characteristics, risk factors, comorbidities, and patient preference. The treatment selected upon relapse will depend on the induction therapy used.

Overall, outcomes in MM have improved dramatically with the introduction of novel therapies active in both the first-line setting and upon relapse. These new regimens are lengthening overall survival and leading to sustained CRs, suggesting that we are nearing a cure.

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