B-Cell Malignancies: Novel Agents, Emerging Treatment Strategies, and the Revolution of Care

Dates of Certification:
November 10, 2014-November 10, 2015

Medium: *Print with online posttest, evaluation, and request for credit*

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Disclosure: *No relevant financial relationships with commercial interests to disclose.*

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Disclosure: Grant/Research Support: *Genentech/ Roche, Pfizer, Puma, Inc. (clinical trial support contracted to University of Southern California);* Consultant: *Eisai, Novartis*

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In the past several years, there has been a veritable explosion in investigational approaches and approval of novel agents for the treatment of B-cell malignancies. These developments and the rapid pace at which novel agents are entering the clinic hold the promise of revolutionizing care and improving outcomes even for high-risk patients with B-cell malignancies. This article covers the key areas in development: CD20 antibodies, BTK inhibitors, P13K inhibitors and chimeric antigen receptor-modified T cells.

Target Audience

This activity is directed toward medical oncologists and hematologists who treat patients with solid tumors and hematologic malignancies. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers may also participate.

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1. Review current standards and emerging data regarding therapies for patients diagnosed with B-cell malignancies
2. Discuss emerging therapies for chronic lymphocytic leukemia

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Introduction

B-cell malignancies comprise a heterogeneous group of hematologic disorders with a diverse spectrum of clinical behavior and characteristics. Traditionally, treatment for B-cell malignancies has consisted of a combination regimen of cytotoxic agents aimed at inducing remission or, in some cases, achieving a cure. While this approach has been relatively efficacious, many of these regimens have been associated with both acute and long-term adverse effects, and for many patients, cure has been elusive.[1]

In the past several years, there has been a veritable explosion of investigational approaches and approval of novel agents for the treatment of B-cell malignancies. These developments and the rapid pace at which novel agents are entering the clinic hold the promise of revolutionizing care and improving outcomes, even for high-risk patients with B-cell malignancies.

CD20 Antibodies

The transmembrane cellular protein CD20 has been validated as a therapeutic target for the treatment of B-cell malignancies.[2] The approval of rituximab, an anti-CD20 monoclonal antibody, revolutionized the treatment of B-cell malignancies, including non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). The addition of rituximab to chemotherapy has been shown to confer a significant survival benefit versus chemotherapy alone for the treatment of NHL and CLL.[2] Although its precise mechanism of action is unclear, rituximab is associated with complement activation; opsonization to macrophages, resulting in antibody-dependent cell-mediated cytotoxicity; and induction of apoptosis.[3]

While rituximab plus chemotherapy has been established as the standard of care for the treatment of NHL and CLL,[2] it has been shown to have limited efficacy as a single agent in CLL.[3] Chemotherapy can be problematic for patients who are not able to tolerate intensive treatment due to advanced age or comorbidities, both of which are common in CLL, which affects mainly elderly patients.[3]

Ofatumumab is a second-generation, fully humanized anti-CD20 antibody that has been approved by the US Food and Drug Administration (FDA) as both a single agent in CLL that is refractory to fludarabine and alemtuzumab, and in combination with chlorambucil for treatment-naïve patients with CLL for whom fludarabine therapy is not an option. Ofatumumab targets a different epitope of CD20 and has a higher binding affinity than rituximab, which results in stronger complement-dependent cytotoxicity. Antibody-dependent cell-mediated cytotoxicity and apoptosis induction are similar among the agents.[3]

In the ongoing phase 3 COMPLEMENT 1 trial in treatment-naïve patients with CLL, the addition of ofatumumab to chlorambucil resulted in enhanced efficacy compared with chlorambucil alone. Median progression-free survival (PFS) was 22.4 months in patients treated with ofatumumab plus chlorambucil versus 13.1 months in those treated with chlorambucil alone (hazard ratio [HR] = 0.57; P <.001), and the incidence rates of adverse events (AEs) considered grade 3 or above were similar in the 2 groups.[4]

The most recent fully human anti-CD20 antibody to enter the market, obinutuzumab (GA101), is associated with more direct cell killing, enhanced antibody-dependent cellular cytotoxicity, and reduced complement-dependent cytotoxicity compared with rituximab and ofatumumab.[5] In the CLL11 study by the German CLL Study Group, 781 treatment-naïve patients with CLL and clinically significant comorbidities were randomly assigned in a 1:2:2 fashion to chlorambucil, chlorambucil plus rituximab, or chlorambucil plus obinutuzumab. Statistically significant improvements in overall response rates (ORRs) and median PFS were found in both the rituximab-plus-chlorambucil arm and the obinutuzumab-plus-chlorambucil arm compared with chlorambucil alone. Median PFS was 16.3 months in patients treated with chlorambucil plus rituximab; 26.7 months in patients treated with chlorambucil plus obinutuzumab; and 11.1 months in those who received chlorambucil alone (P <.001, both combination arms vs chlorambucil monotherapy). Treatment with obinutuzumab plus chlorambucil also resulted in higher rates of molecular response and complete response (CR) compared with chlorambucil plus rituximab (20.7% vs 7%; P <.001).[6] Updated data demonstrated an overall survival (OS) benefit with chlorambucil plus obinutuzumab versus chlorambucil alone (9% deaths in the chlorambucil-plus-obinutuzumab arm vs 20% deaths for the chlorambucil-alone arm; HR = 0.41; P =.002).[5] Although infusion-related adverse reactions and neutropenia occurred more commonly in patients who received obinutuzumab plus chlorambucil than in those in the rituximab-plus-chlorambucil arm, the risk of infection was not increased.[6]

Following early-phase 1/2 trials that suggested a dose response with obinutuzumab, the phase 2 multicenter, randomized GAGE trial sought to compare the safety and efficacy of 1000 mg of obinutuzumab (n = 41) versus 2000 mg of obinutuzumab (n = 39) in treatment-naïve patients with CLL. Single-agent effi-

TABLE. Selected Clinical Trials of Ibrutinib for B-Cell Malignancies[19]

Trial	Type	Agent(s)	Primary Outcome Measures	NCT Trial No.
Ibrutinib and Combination Chemotherapy in Treating Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Phase 1	Ibrutinib Rituximab Ifosfamide Carboplatin Etoposide	Safety of ibrutinib in combination with rituximab-ifosfamide, carboplatin, and etoposide (R-ICE) Establishment of maximum tolerated dose of ibrutinib with R-ICE	NCT02219737
Ibrutinib Versus Ibrutinib + Rituximab (i vs iR) in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL)	Phase 2	Ibrutinib Rituximab	PFS	NCT02007044
Ibrutinib in Treating Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma in Patients With HIV Infection	Phase 1	Ibrutinib	Incidence of toxicities Maximum tolerated dose of ibrutinib	NCT02109224
Study of the Bruton's Tyrosine Kinase Inhibitor in Combination With Rituximab in Previously Untreated Subjects With Follicular Lymphoma	Phase 2	Ibrutinib Rituximab	ORR	NCT01980654

ORR, overall response rate; PFS, progression-free survival.

cacy was demonstrated at both dosages, with a difference in ORR between the 2 arms favoring the higher dosage (49% vs 67%; *P* =.08). No new safety concerns emerged, although further study is warranted to determine long-term side effects.[7]

BTK Inhibitors

Elucidation of the role of Bruton's tyrosine kinase (BTK) in B-lymphocyte development, differentiation, signaling, and survival has augmented understanding of the mechanisms underlying the development of B-cell malignancies.[8] BTK, which is required for B-cell receptor signaling, has been implicated in the development of the most common B-cell malignancies, including CLL, mantle cell lymphoma (MCL), follicular lymphoma, diffuse large B-cell lymphoma, and acute lymphocytic leukemia.[8]

Ibrutinib is a potent inhibitor of BTK[9] that was first approved by the FDA in 2013 for the treatment of MCL in patients who have received at least 1 prior therapy; the FDA expanded the approved use of ibrutinib in July 2014 to include the treatment of patients with CLL who carry a deletion in chromosome 17 (17p deletion), which has been linked to poor outcomes with standard treatments.[10]

Pivotal findings from the international phase 3 randomized RESONATE trial (N = 391) demonstrated that ibrutinib significantly improved PFS compared with ofatumumab in patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL). The primary end point of the study was PFS; secondary end points included OS, ORR, and safety.[11] Patients were randomized to receive either 420 mg of oral ibrutinib (n = 195) once daily or intravenous ofatumumab (n = 196, initial dose of 300 mg followed by 11 doses at 2000 mg per dose and schedule consistent with local labeling) for up to 24 weeks, or until progression or unacceptable toxicity occurred. Ibrutinib patients had received a median of 3 prior therapies versus 2 prior therapies in the ofatumumab arm.[11] After a median follow-up of 9.4 months, ibrutinib significantly improved PFS (median not reached vs 8.1 months; HR = 0.215; *P* <.0001; 78.5% risk reduction) and OS (median not reached; HR = 0.434; *P* = .0049) compared with ofatumumab. Overall response rate was 42.6% in the ibrutinib arm versus 4.1% in the ofatumumab arm (*P* <.0001), and ORR plus partial response with lymphocytosis was 62.6% versus 4.1% in the ibrutinib and ofatumumab arms, respectively.[11] AEs that occurred more frequently in the ibrutinib arm compared with the ofatumumab arm included diarrhea (47.7% vs 17.8%), nausea (26.2% vs 18.3%), and atrial fibrillation (5.1% vs 0.5%), whereas fatigue was comparable in the ibrutinib versus the ofatumumab arm (27.7% vs 29.8%). The rate of drug discontinuations due to AEs was 4.1% in the ibrutinib arm versus 3.6% in the ofatumumab arm.[11] Numerous clinical trials of ibrutinib in B-cell malignancies are ongoing (**Table**).

P13K Inhibitors

PI3K-delta signaling occupies a prominent role in the activation, proliferation, and survival of B cells, and has been found to be overactive in numerous B-cell malignancies. PI3K-delta inhibition reduces B-cell survival by affecting many essential pathways and suppressing the homing and retention of malignant B-cells in lymphoid tissues.[12]

Idelalisib is a first-in-class, targeted, highly selective oral inhibitor of PI3K-delta[13] that was approved in July 2014 for the treatment of relapsed CLL in combination with rituximab in patients for whom rituximab monotherapy would be considered appropriate due to comorbidities. It also received accelerated approval for patients with relapsed SLL or follicular B-cell non-Hodgkin lymphoma who have received at least 2 prior systemic therapies.[14]

A phase 3, randomized, double-blind, placebo-controlled trial assessed the safety and efficacy of combination therapy with idelalisib or placebo with rituximab in patients with relapsed CLL who were unable to undergo standard chemotherapy. The trial's primary end point was PFS, and secondary end points were ORR and CR, lymph-node response, and OS.[15] The combined treatment regimen of idelalisib and rituximab resulted in statistically significant improvement in PFS compared with placebo and rituximab, with a 93% rate of PFS at 24 weeks compared with 46% in the placebo arm. Progression of disease occurred in 12 patients in the idelalisib arm versus 53 patients in the placebo arm. OS was also superior in the idelalisib arm compared with the placebo arm (92% vs 80% at 12 months), with an adjusted HR for death of 0.28 (95% confidence interval [CI], 0.09-0.86; P =.02). Median duration of OS was not reached at the time of analysis.[15] AEs occurred in more than 90% of study participants. The most common AEs in patients receiving idelalisib plus rituximab were pyrexia, fatigue, nausea, chills, and diarrhea. AEs were similar in the placebo group, with the most common being infusion-related reactions, fatigue, cough, nausea, and dyspnea. The majority of AEs were grade 2 or lower. At least 1 serious AE was reported by 44 patients (40%) in the idelalisib group and by 37 patients (35%) in the placebo group. The most frequent serious AEs were pneumonia, pyrexia, and febrile neutropenia.[15]

A second PI3K inhibitor, IPI-145, is currently in advanced clinical trials for CLL, follicular lymphoma, and other B-cell malignancies.[5,19]

Chimeric Antigen Receptor–Modified T Cells

The potential for the adoptive transfer of T cells to target malignancy is an emerging treatment strategy that has been demonstrating efficacy in clinical trials.[5,16] This treatment involves the use of T cells that have been engineered to express a chimeric antigen receptor (CAR) that targets CD19 (CTL019), a B-cell restricted marker.[16] Just 1 treatment with engineered gene-modified T cells has been found to have the potential to generate potent and long-lasting antitumor immunity.[16]

Early data from an ongoing phase 2 trial of CTL019 demonstrated potent antitumor effects in patients with advanced, relapsed/refractory CLL. Median follow-up as of July 15, 2013, was 3 months for the 27 patients then enrolled and 3.3 months for responding patients. Two patients had achieved CR and 2 patients had achieved partial response (PR), both with clearance of CLL from the blood and marrow and >50% reduction in adenopathy, for an ORR of 40%. No responding patient had progressed.[17]

Toxicities are an expected occurrence with autologous T-cell transfer, highlighting the need for effective AE management strategies.[5] If the end points of the trials continue to be similar to those of the 3-month follow-up and the FDA agrees, CTL019 therapies are expected to become commercially available sometime between 2016 and 2020.[18]

Conclusion

The investigation of novel agents and treatment strategies in B-cell malignancies has led to significant and clinically meaningful advances in the care of patients with these diseases. While chemotherapy remains the mainstay of treatment for hematologic malignancies, the recent flurry of FDA approvals on the basis of unprecedented HRs, as well as the range o–f novel agents under investigation, are contributing to the expansion of the treatment armamentarium for patients with B-cell malignancies.

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