Targeted Approaches to the Management of Follicular Lymphoma

The treatment of follicular lymphoma has changed dramatically over the past several years. The availability of newer, novel forms of therapy has enabled the field to continue to evolve. In addition to having tumor-specific activity, these newer agents provide the possibility of a more favorable toxicity profile than conventional chemotherapy.

Introduction

As the second most common form of non-Hodgkin lymphoma (NHL), follicular lymphoma affects thousands of new patients in the United States each year. Although follicular lymphoma is considered an indolent disease, its clinical course is highly variable. Asymptomatic patients with low tumor burden can be monitored closely with the “watch and wait” strategy, given that the early intervention of chemotherapy or immunotherapy has not demonstrated a survival benefit.[1,2] The most widely accepted indications for treatment are one or more of the following criteria from the Groupe d'Étude des Lymphomes Folliculaires (GELF): a single lesion > 7 cm, three nodal sites > 3 cm, splenomegaly, effusions, threat or evidence of organ compression, or constitutional symptoms.[3] Whereas patients with limited-stage disease have several treatment options—including single-agent rituximab, radiation, and chemoimmunotherapy, those with advanced-stage disease typically receive chemoimmunotherapy.[4,5] Both the German Study Group Indolent Lymphomas (StiL) NHL-2 study and the pharmaceutical company–sponsored Bendamustine Rituximab Investigational Non-Hodgkin's Trial (BRIGHT) have established the front-line role of combination therapy with bendamustine and rituximab in the treatment of follicular lymphoma, based on comparable efficacy and better tolerability than standard regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).[6,7] Despite high response rates with initial therapy, follicular lymphoma is characterized by frequent relapses, and patients need improved treatment options.

Since the discovery of rituximab, there has been significant innovation in drug development, based on a greater understanding of the pathogenesis of the disease. The multistep process leading to follicular lymphoma is theorized to begin with an initial genetic insult, the hallmark t(14;18) translocation, which results in overexpression of the anti-apoptotic B-cell lymphoma protein, BCL-2.[8] This translocation is not the sole factor in malignant transformation, as it is a naturally occurring anomaly, often identified in healthy individuals. Furthermore, preclinical studies have indicated a positive correlation between increasing numbers of genetic alterations and the progression from follicular lymphoma in situ to grade 3A follicular lymphoma.[9] The B-cell receptor is a critical cellular factor in the development of the disease. Its active tonic signaling leads to recruitment of the spleen tyrosine kinase (SYK) and activation of multiple downstream pathways, including phosphatidylinositol 3-kinase (PI3K), nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB), and mitogen-activated protein kinase (MAPK). Activation of these pathways ultimately results in the maturation, proliferation, and survival of malignant lymphocytes.[10] Other key components include immune cells such as T cells, dendritic cells, and reticular cells, which infiltrate among the centrocytes.[11] In addition to stimulating the B-cell receptor, these immune cells induce exhaustion of cytotoxic T cells and allow for T-cell evasion via disruption of synapses and secretion of interleukin-12.[12] Expression of the inhibitory receptor programmed cell death 1 (PD-1) is another contributing factor, as its presence is believed to affect the ability of T cells to mount appropriate antitumor responses.[13] Several novel therapies have been developed to target these various aspects of the disease in the hope of identifying more effective, yet tolerable, treatment options for patients with follicular lymphoma. (See the Table for a summary of therapies approved and in development for treatment of follicular lymphoma.)
Antibody-Based Therapy

Newer anti-CD20 monoclonal antibodies

Since the approval of rituximab, there has been significant investigation into the development of a superior anti-CD20 monoclonal antibody. Second- and third-generation versions vary in their structures and mechanisms of action. Two anti-CD20 antibodies, ofatumumab and obinutuzumab, have been approved by the US Food and Drug Administration (FDA) for indications in chronic lymphocytic leukemia (CLL). Ofatumumab, a type I human monoclonal antibody, was initially approved for patients whose disease is refractory to fludarabine and alemtuzumab.[14] Obinutuzumab was approved in combination with chlorambucil for patients with preexisting comorbidities that preclude conventional chemoimmunotherapy.[15] Although designed to induce stronger complement-dependent cytotoxicity than rituximab, ofatumumab demonstrated minimal activity in rituximab-refractory follicular lymphoma (overall response rate [ORR], 10% to 13%; median progression-free survival [PFS], 5.8 months).[16] In phase II trials of ofatumumab in combination with chemotherapy, including bendamustine and CHOP, results appeared comparable to those achieved with rituximab-based regimens, although no direct comparisons have been made.[17,18]

Obinutuzumab, a type II glycoengineered humanized antibody, is further in development for use in NHL. This agent, which works primarily by triggering antibody-dependent cellular cytotoxicity (ADCC) and apoptosis, has demonstrated superiority to rituximab in preclinical studies, including those employing whole blood B cell–depletion assays, human lymphoma xenograft mice models, and nonhuman primates.[19] When compared with rituximab in patients with indolent B-cell NHL, obinutuzumab produced a higher ORR by independent radiology review (45% vs 27%; P = .01); however, complete response (CR) and PFS rates were similar.[20] Like ofatumumab, treatment with obinutuzumab is associated with a higher rate of infusion-related reactions than rituximab (grade 1-4, 72% vs 49%; and grade 3/4, 11% vs 5%, respectively). In contrast to ofatumumab, it has efficacy in rituximab-refractory indolent NHL, producing an ORR of 50% and median PFS of 12 months among 10 patients.[21] The phase III GADOLIN study evaluated obinutuzumab in combination with bendamustine followed by maintenance obinutuzumab in the same disease setting (N = 413).[22] While the response rates by independent review were similar to those observed in the comparative arm of patients randomized to single-agent bendamustine (bendamustine-obinutuzumab ORR, 69% [CR, 11%] vs bendamustine alone ORR, 63% [CR, 12%]), the median PFS was significantly higher with the combination (not reached vs 14.9 months; P = .00011). Treatment with the combination of bendamustine and obinutuzumab was associated with a similar incidence of grade ≥ 3 adverse events compared with bendamustine monotherapy (68% vs 62%), which included neutropenia (33% vs 26.3%) and infusion-related reactions (9% vs 3.5%). While there was no difference in overall survival (OS) noted, the study did demonstrate the clinical benefit of obinutuzumab in rituximab-refractory disease. The role of the drug in this setting is becoming less clear, as more patients now receive bendamustine-rituximab as front-line therapy. In the phase Ib GAUDI study, bendamustine-obinutuzumab and obinutuzumab-CHOP produced similar response rates in patients with previously untreated follicular lymphoma, with ORRs of 93% (CR, 39%) and 95% (CR, 35%), respectively.[23] The incidences of grade 3/4 neutropenia and infection were similar to historical data on rituximab chemotherapy. These data prompted the front-line phase III GALLIUM study of chemotherapy (CHOP, CVP [cyclophosphamide, vincristine, and prednisone], or bendamustine) with obinutuzumab or rituximab followed by maintenance obinutuzumab or rituximab in advanced-stage indolent B-cell NHL (ClinicalTrials.gov identifier: NCT01332968). Newer monoclonal antibodies directed against CD20, such as ublituximab, and rituximab biosimilars are also in development.

Monoclonal antibodies to alternative targets

Monoclonal antibodies directed against other B-cell antigens have also been developed. Galiximab, a chimeric human-macaque anti-CD80 antibody, and epratuzumab, a humanized anti-CD22 antibody, were two of the first antibodies directed against these targets to be explored in follicular lymphoma. Both antibodies have shown activity as single agents and in combination with rituximab in follicular lymphoma. However, neither is being studied further due to the availability of newer, more promising therapies.[24-28] MEDI-551, an afucosylated humanized anti-CD19 antibody, induces cell death via ADCC and cytotoxic T-cell response. The lack of a fucose moiety on the Fc portion of the antibody is believed to enhance the activity of ADCC. Phase I studies of MEDI-551 in heavily
pretreated follicular lymphoma have reported ORRs ranging from 31% to 82%.[29,30] The median PFS from the earlier study was nearly 10 months. MEDI-551 is currently being evaluated in aggressive lymphomas in combination with rituximab and salvage chemoimmunotherapy (ClinicalTrials.gov identifiers: NCT00983619 and NCT01453205). Also targeting CD19 is MOR208, a humanized monoclonal antibody that has been engineered to have a higher affinity to FcγRIIa and FcγRIIa, resulting in stronger ADCC. In a phase II study of patients with relapsed and refractory B-cell NHL who had received a median of two prior therapies, the ORR was 26% among those with follicular lymphoma (n = 31).[31] The median duration of response (DOR) was 2.6 months; however, the longest DOR was 15.4 months. Upcoming trials with MOR208 include combination studies with lenalidomide in diffuse large B-cell lymphoma (DLBCL) and CLL (ClinicalTrials.gov identifiers: NCT02399085 and NCT02005289).

Radioimmunotherapy

One of the first attempts to improve upon the efficacy of the naked monoclonal antibody was radioimmunotherapy, which produced ORRs of 65% to 74% in patients with relapsed and refractory indolent B-cell lymphomas.[32,33] 90Y-ibritumomab tiuxetan, the first radioimmunotherapy to receive FDA approval, was approved in February 2002 for relapsed or refractory low-grade, follicular, or transformed B-cell NHL. In 2009, it was granted expanded approval as consolidation therapy in previously untreated follicular lymphoma patients with a partial or complete response to first-line chemotherapy. 131I-tositumomab was approved in June 2003 (along with tositumomab) for CD20-positive follicular NHL, with and without transformation, in relapsed rituximab-refractory patients with relapse following chemotherapy. The use of 131I-tositumomab and 90Y-ibritumomab tiuxetan has declined significantly over the past several years; the manufacture and sale of 131I-tositumomab (marketed in the United States and Canada as Bexxar) was stopped in February 2014. Radioimmunotherapy can be difficult; there are strict hematologic criteria (< 25% lymphomatous marrow involvement, platelet count > 100 x 10^9, leukocyte count > 1.5 x 10^9), and its administration requires a certified nuclear medicine physician. In addition, the patient must not have had prior radiation to > 25% of the bone marrow nor undergone stem cell transplantation.[34]

Antibody-drug conjugates (ADCs)

Recent efforts in augmenting antibody-based therapy include the use of ADCs. Once bound to its target antigen, the ADC is engulfed via endocytosis, trafficked to the lysosome for degradation, and ultimately released, whereupon it causes damage to tubulin and DNA. The calicheamicin-bound anti-CD22, inotuzumab ozogamicin, was one of the first to be studied in patients with follicular lymphoma who were refractory to CD20-targeted therapy, yielding an ORR of 66%.[35] The ORR increased to 87% when inotuzumab ozogamicin was combined with rituximab in patients with relapsed and refractory follicular lymphoma, prompting a trial in which it was compared with combination treatment with rituximab plus chemotherapy.[36] The trial was closed early due to poor accrual. Inotuzumab ozogamicin is currently being studied in combination with the mammalian target of rapamycin (mTOR) inhibitor temsirolimus in relapsed and refractory CD22-expressing NHL (ClinicalTrials.gov identifier: NCT01535989). Pinatuzumab vedotin and polatuzumab vedotin, which target CD22 and CD79b, respectively, are ADCs linked to the anti-tubulin molecule monomethyl auristatin E. While both agents have demonstrated activity in indolent NHL (with reported ORRs of 50% and 47%, respectively), polatuzumab vedotin is being taken further in development.[37,38] When polatuzumab vedotin was administered at a higher dose (2.4 mg/kg) with rituximab in patients with relapsed and refractory follicular lymphoma (n = 25), the ORR was 76% (CR, 44%) and median PFS was 15 months.[39] The cohort of 20 patients treated at the lower rituximab dose (1.8 mg/kg) had a similar response rate (ORR, 70%; CR, 40%), and median PFS and DOR were not reached. Peripheral neuropathy, a common toxicity with ADCs, occurred less frequently with the lower dose of polatuzumab vedotin and was ameliorated in some patients by dose delay and reduction. Ongoing studies with polatuzumab vedotin include phase I/II combinations with bendamustine-rituximab or obinutuzumab-bendamustine in relapsed and refractory follicular lymphoma (ClinicalTrials.gov identifier: NCT02257567) and R-CHOP in B-cell NHL patients who have received less than one prior therapy (ClinicalTrials.gov identifier: NCT01992653). Coltuximab ravtansine (formerly SAR3419) is an anti-CD19 ADC that has also been associated with neurologic complications, primarily dose-limiting ocular toxicity.[40] IMGN529, which targets the overexpressed CD37 protein, is another B-cell–directed ADC in development.[41]
**PI3K inhibitors**

In contrast to the various antibody-based therapies under investigation for treatment of follicular lymphoma, several small molecules have been designed to inhibit key intracellular pathways of the malignant B cell. The majority of these agents are directed against kinases downstream of the B-cell receptor, and many have been combined with bendamustine-rituximab, given this combination’s efficacy and tolerability. Idelalisib, a potent PI3K-δ inhibitor, was the first PI3K inhibitor to be approved by the FDA for follicular lymphoma. It received an indication for patients who have received at least two prior systemic therapies, based on results of a phase II study in rituximab-refractory indolent NHL.[42] As reported at the 2015 American Society of Clinical Oncology Annual Meeting, of the 72 patients in the study who had follicular lymphoma, 54% were considered high-risk by the Follicular Lymphoma International Prognostic Index.[43] The patients had received a median of four prior therapies, and 86% had disease that was refractory to the last regimen they received. The ORR was 56% and the median PFS was 11 months. The median PFS for the 10 patients who achieved a CR was 27 months. Notable grade 3/4 adverse events included neutropenia (27% of all patients), diarrhea/colitis (16%), elevations in hepatic transaminases (13%), and pneumonia (7%). Idelalisib was subsequently administered with rituximab, bendamustine, and bendamustine-rituximab in a phase I study of patients with relapsed (n = 79) and refractory (n = 59) indolent NHL, the majority of whom had follicular lymphoma.[44] The ORRs were similar between the arms (75% to 88%); however, treatment with bendamustine-rituximab-idelalisib was associated with the highest CR (43%) and longest median PFS (37.1 months). A phase III trial of bendamustine-rituximab with or without idelalisib in relapsed and refractory indolent B-cell NHL is ongoing (ClinicalTrials.gov identifier: NCT01732926). In phase I investigations, combined treatment with idelalisib and lenalidomide plus the second-generation SYK inhibitor entospletinib has demonstrated considerable toxicity, including hepatic transaminitis, sepsis, and refractory pneumonitis.[45,46] Second-generation PI3K inhibitors, including duvelisib (IPI-145), TGR-1202, and INCB040093, are in development. Duvelisib, a dual inhibitor of the delta and gamma isoforms of PI3K, has demonstrated an ORR of 69% (CR, 38%) in a heavily pretreated follicular lymphoma cohort (n = 13).[47] Based on these encouraging data, duvelisib is being administered with rituximab or obinutuzumab in patients with previously untreated follicular lymphoma (ClinicalTrials.gov identifier: NCT02391545) and with bendamustine and/or rituximab in those with relapsed B-cell malignancies (ClinicalTrials.gov identifier: NCT01871675).

**Bruton tyrosine kinase (BTK) inhibitors**

Ibrutinib, a selective and irreversible inhibitor of BTK, may also have some impact on the tumor microenvironment via cytokine and chemokine inhibition.[48] Approved in CLL, mantle cell lymphoma, and Waldenström macroglobulinemia, it has demonstrated activity in a number of B-cell malignancies.[49-53] In a phase II study of relapsed and refractory follicular lymphoma, ibrutinib yielded an ORR of 30% (with one CR) and a median PFS of 9.9 months. The 40 enrolled patients had received a median of three prior therapies, and 36% were considered refractory to treatment. Common adverse events included mild diarrhea, rash, and fatigue; rare events included atrial fibrillation and bleeding.[54] Like idelalisib, ibrutinib has been combined with bendamustine-rituximab in the treatment of B-cell NHL.[55] This triplet produced an ORR of 90% (CR, 50%) in a cohort of 10 patients with previously treated follicular lymphoma. At the time these results were reported, the median PFS had not been reached. Notable grade 3/4 adverse events included neutropenia (33%), rash (25%), and thrombocytopenia (19%). Results from SELENE, a randomized phase III trial of ibrutinib with bendamustine-rituximab or R-CHOP in previously treated follicular lymphoma and marginal zone lymphoma, will provide more insight into the role of ibrutinib in the management of indolent NHL (ClinicalTrials.gov identifier: NCT01974440). Phase I trials of combinations with targeted agents include the Alliance for Clinical Trials in Oncology study of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma[56] and the pharmaceutical-sponsored trial of combination therapy with ublituximab, TGR-1202, and ibrutinib in relapsed and refractory B-cell malignancies.[57] Second-generation BTK inhibitors, including ACP-196 and ONO-4059, are also in development.

**B-cell lymphoma-2 (BCL-2) inhibitors**

The chromosomal translocation t(14;18) allows for dysregulation of the BCL-2 oncogene and overexpression of the anti-apoptotic BCL-2 family of proteins, contributing to development of follicular lymphoma. Venetoclax, formerly known as ABT-199, is a second-generation selective BCL-2
inhibitor in the early stages of clinical investigation. When this agent was administered at a dose greater than 600 mg daily to six patients with relapsed and refractory follicular lymphoma, three patients achieved a response.[58] Common toxicities reported included mild nausea (34%) and diarrhea (25%), and grade 3/4 myelosuppression occurred in less than 15% of patients. Two patients (one with DLBCL and one with mantle cell lymphoma) in the entire NHL cohort (of 44 patients then enrolled in the study) developed laboratory evidence of grade 3 tumor lysis syndrome. When venetoclax was combined with bendamustine-rituximab in 21 patients with relapsed and refractory follicular lymphoma, the ORR was 71% (CR, 29%).[59] While a maximum tolerated dose was not reached, dose-limiting toxicities included thrombocytopenia, neutropenia, and Stevens-Johnson syndrome. Venetoclax is being evaluated in relapsed and refractory follicular lymphoma, in a three-arm phase II study of bendamustine-rituximab vs rituximab-venetoclax vs bendamustine-rituximab-venetoclax (ClinicalTrials.gov identifier: NCT02187861). It will be studied with ibrutinib in a phase I/II trial of relapsed follicular and marginal zone lymphoma (Ujjani C, principal investigator). Small-molecule inhibitors aimed at less well known targets are also under investigation, including selinexor (a selective inhibitor of nuclear export), MK-2206 (an AKT inhibitor), alisertib (an Aurora-A kinase inhibitor), and cerdulatinib (a dual SYK/Janus tyrosine kinase [JAK] inhibitor).

TO PUT THAT INTO CONTEXT

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What Are the Challenges of Treating Follicular Lymphoma?
Follicular lymphoma, the most common indolent lymphoma, is characterized by high rates of initial response to chemoimmunotherapy, but it is not curable with standard therapy. The clinical course of the disease is highly variable and somewhat unpredictable. As a result, the optimal management of follicular lymphoma, including the most effective sequencing of therapy, is undefined. Identifying the subsets of patients at risk for early failure and those with indolent disease that remains quiescent would assist clinicians in tailoring therapy for individual patients. Given the heterogeneity of treatment options and possible clinical outcomes, improvement in risk stratification and personalization in follicular lymphoma is needed, particularly given the expanding treatment options outlined by Dr. Ujjani.

What Can We Expect in the Future?
Historically, prognostication for patients with follicular lymphoma has relied primarily on clinical characteristics. The Follicular Lymphoma International Prognostic Index (FLIPI) can distinguish patients with low or intermediate risk from those at high risk, but it is not routinely used to guide risk-adapted therapy. More recently, the development of m7-FLIPI, a multivariable risk model incorporating the mutation status of seven genes with established clinical relevance in follicular lymphoma, improved the ability to predict early treatment failure in patients receiving front-line chemoimmunotherapy. Identifying the follicular lymphoma patients at highest risk for early treatment failure with standard therapy allows for their prioritization to a clinical trial assessing some of the novel therapies outlined by Dr. Ujjani.

Given the number of therapeutic agents under investigation in follicular lymphoma, and the vast combinatorial possibilities, consideration of toxicity is as imperative as the need to conduct correlational studies to unravel the complexity of this disease.
Tumor Microenvironment

Immunomodulatory agents

As stated previously, the tumor microenvironment plays a critical role in the pathogenesis of follicular lymphoma. Approaches to promoting a functional immune system have allowed for effective treatment of the disease. The second-generation immunomodulatory agent lenalidomide has been the most extensively studied of these therapies. Its mechanisms of action include activation of natural killer cells and T cells, stimulation of apoptosis, and inhibition of tumor necrosis factor (TNF-α) and vascular endothelial growth factor (VEGF).[60] In follicular lymphoma cell lines, lenalidomide has been shown to restore immunologic synapses between malignant lymphocytes and T cells and augment rituximab-mediated ADCC.[61] Lenalidomide has demonstrated modest activity as a single agent in relapsed or refractory follicular lymphoma (with ORRs ranging from 27% to 49%); however, when lenalidomide was added to rituximab the ORR improved to 76% and the median event-free survival time was 2 years.[62,63] The doublet (dubbed “R2,” for Revlimid [lenalidomide] plus rituximab) was evaluated by the Alliance study as a front-line regimen, producing an ORR of 93% (CR, 72%) and 2-year PFS of 89% (n = 65).[64] Minimal toxicity was noted with the regimen; common grade 3/4 adverse events included neutropenia (in 19% of patients), rash (8%), and infection (8%). In a similar study from the University of Texas MD Anderson Cancer Center, 35 of the 50 patients with follicular lymphoma achieved a CR (70%) and 5 had an unconfirmed CR.[65] The Swiss Group for Clinical Cancer Research and the Nordic Lymphoma Group reported an ORR of 78% (CR, 61%) with the R2 combination (n = 77).[66] The impressive activity noted in the Alliance and MD Anderson studies prompted the pharmaceutical-sponsored phase III RELEVANCE trial of R2 vs rituximab with chemotherapy (CVP, CHOP, or bendamustine) in previously untreated advanced-stage follicular lymphoma (ClinicalTrials.gov identifier: NCT01650701). R2 has been studied in combination with other regimens such as CHOP, producing an ORR of 94% (CR/unconfirmed CR, 74%) in patients with previously untreated follicular lymphoma.[67] These data are relatively comparable to previously reported results with R2 and call into question the need for CHOP. The Alliance has conducted subsequent studies of R2 with targeted agents including ibrutinib and idelalisib. Results with ibrutinib are pending; however, the trial of idelalisib was closed owing to considerable toxicity.[45,56] Lenalidomide has also been combined with obinutuzumab in the treatment of relapsed and refractory disease, yielding an ORR of 68% (CR, 35%) among the 20 patients enrolled in the phase I portion of a phase I/II study.[68]

Immune checkpoint modulators

In patients with follicular lymphoma, the overexpression of PD-1 in the intratumoral T cells results in an impairment in antitumor immune surveillance. Inhibition of PD-1 or its ligands, PD-L1 and PD-L2, has shown promise in the treatment of follicular lymphoma. Pidilizumab, a humanized PD-1 monoclonal antibody, was the first PD-1 inhibitor to be explored. Although minimally active as a single agent, when pidilizumab was administered in conjunction with rituximab in the setting of relapsed follicular lymphoma, the ORR was 66% and median PFS was 18.8 months (n = 29).[69,70] The majority of the responses were complete (52%), and the median PFS had not been reached for those who achieved a response. Nivolumab, a fully human monoclonal antibody approved for the treatment of melanoma and squamous non–small-cell lung cancer, has also demonstrated activity in relapsed and refractory follicular lymphoma. A phase I evaluation has reported an ORR of 40% (CR, 10%) in 10 patients.[71] Nivolumab is currently being studied in combination with ibrutinib in patients with relapsed B-cell malignancies (ClinicalTrials.gov identifier: NCT02329847). Pembrolizumab and MEDI-0680 are humanized PD-1 antibodies also under clinical investigation in CLL and other low-grade B-cell NHLs, as well as in relapsed and refractory aggressive B-cell lymphomas (ClinicalTrials.gov identifiers: NCT02332980 and NCT02271945, respectively). MEDI4736, a human anti–PD-L1 antibody, is also being studied with ibrutinib in patients with relapsed lymphoma (ClinicalTrials.gov identifier: NCT02401048). Similar to PD-1, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a negative regulator of T-cell function. Inhibition of CTLA-4 with ipilimumab, also approved in melanoma, has demonstrated some activity in lymphoid malignancies, including in one patient with follicular lymphoma.[72]

Bispecific T-cell engager (BiTE)

The BiTE is a unique form of immunotherapy that stimulates T-cell function via binding simultaneously to CD3 on the surface of the T cell and a specific marker on the malignant B cell,
resulting in caspase-mediated apoptosis. Blinatumomab, a CD19-specific BiTE approved for treatment of relapsed and refractory B-cell acute lymphoblastic leukemia (ALL), has demonstrated activity in other CD19-positive lymphoid diseases.[73] It produced an ORR of 100% in a phase I study of 13 patients with relapsed indolent NHL, the majority of whom had a follicular or mantle cell histology.[74] Four patients achieved a CR, and eight remained in remission at 13 months. A single cycle of blinatumomab requires a 4-week continuous IV infusion and is associated with significant, yet reversible, neurologic toxicity. The current focus of clinical investigations with this agent is ALL, and its role in follicular lymphoma is unclear.

**Chimeric antigen receptor (CAR)-modified T cells**

CAR-modified T cells are one of the newest, most intriguing, forms of immunotherapy. These autologous T cells have been genetically transduced using lentiviral vectors to express tumor cell-specific antigen receptors. Having demonstrated activity in CLL and ALL, CAR-modified T cells are now being explored in CD19-positive NHL. A phase II study at the University of Pennsylvania demonstrated an ORR of 100% among seven patients with relapsed and refractory follicular lymphoma who lacked curative treatment options.[75] Six patients achieved a CR by 6 months, and responses appeared to be durable. In all seven patients there was evidence of severe cytokine release syndrome (cytokine storm); in two of the patients this was a grade 3/4 toxicity. One patient developed grade 5 encephalopathy 2 months after completing therapy. Although quite promising, further investigation is necessary to fully understand this new method.

**Conclusion**

The treatment of follicular lymphoma has changed dramatically over the past several years. The availability of newer, novel forms of therapy has enabled the field to continue to evolve. In addition to having tumor-specific activity, these newer agents provide the possibility of a more favorable toxicity profile than conventional chemotherapy. Although chemoimmunotherapy has been the traditional front-line induction for patients with advanced-stage disease, this concept is being challenged by the remarkable efficacy of the R² regimen (with ORR > 90%; CR, 61% to 72%).[64,66] If the phase III RELEVANCE trial demonstrates results with R² that are even equivalent to those achieved with standard regimens such as R-CHOP or bendamustine-rituximab, a major paradigm shift will occur; R² would then be the first chemotherapy-free option for the initial treatment of follicular lymphoma. Given that the attainment of a CR has been associated with a survival benefit in this setting, there is still room for improvement.[76] Although approved as a single agent, idelalisib is being studied in combination with rituximab in previously untreated and relapsed patients (ClinicalTrials.gov identifiers: NCT02258529 and NCT01732913). Ongoing clinical investigations, such as the Alliance phase I trial of R² plus ibrutinib in previously untreated patients, are exploring the benefit of multitargeted agents in this population. Studies such as the phase II trial of bendamustine-rituximab vs rituximab-venetoclax vs bendamustine-rituximab-venetoclax are exploring the utility of other targeted agents in comparison to standard chemoimmunotherapy. While the concept of multitargeted therapy is quite appealing, these regimens must be explored with caution. Early-phase investigations of idelalisib with R² and entospletinib produced significant adverse events, requiring study closures.[45,46] In addition to understanding how to combine treatment with these agents safely and efficaciously, research efforts must incorporate sound correlative science. Through whole-exome sequencing, Woyach et al have already discovered mutations associated with resistance to ibrutinib in CLL.[77] The identification of other predictive biomarkers is imperative to tailor therapy effectively and to develop superior regimens for individual patients. Furthermore, this information may enable us to provide appropriate treatment options that are also financially prudent. Given the lengthy follow-up period required to achieve the traditional objectives of clinical trials, it is important to explore earlier, yet meaningful, surrogate endpoints. Residual positron emission tomography activity on post-induction imaging, the presence of minimal residual disease, and relapse within 2 years of chemoimmunotherapy have been associated with an inferior PFS and OS outcome; in contrast, the presence of a CR at 30 months has been correlated with a significantly reduced risk of progression in patients with follicular lymphoma.[78-81] By incorporating novel therapies into innovative clinical investigations, we may achieve significantly better outcomes and improve the outlook for patients with this incurable disease.

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Table: Targeted Therapies in Development and FDA-Approved for the Tre...


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