Overview

This text-based CME activity provides guidance and expert recommendations on the initial diagnostic workup and therapy selection, as well as an overview of the latest data on recently approved and emerging therapeutic options for patients with B-cell non-Hodgkin lymphoma (NHL). Although recent treatment advances do not provide a cure, they do, however, provide longer remissions and improve patient outcomes. We invite you to learn more about the current standard of care, recently approved treatment options, including PI3K inhibitors, as well as safety and efficacy data from the select clinical trials.

Content Areas

- Presentation and workup
- Advancing the treatment paradigm
- PI3K pathway inhibitors
- Other select new therapy strategies for B-cell NHL-defining soft tissue sarcoma (STS)

Section

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Target Audience

This activity was developed for hematologists/oncologists, hematologists, medical oncologists and other health care providers who care for patients with non-Hodgkin Lymphoma (NHL).

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Apply NCCN practice guidelines, expert recommendations, and/or the outcomes of clinical trials to select the optimal treatment for patients with indolent or aggressive NHL throughout the course of the disease
- Evaluate the clinical efficacy and safety data from trials of PI3K inhibitors

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Advances in the Management and Treatment of Non-Hodgkin Lymphoma

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative disorders that originate from lymphocytes at various stages of development. Although T-cells and natural killer cells can give rise to NHL, the most common (85%–90%) types are derived from B-cell lineages.[1,2] Among the B-cell lymphomas, distinct subtypes have been identified based on cell of origin, immunohistochemistry, genetic profile, and clinical features.[2,3] **Diffuse large B-cell lymphoma (DLBCL)** and **follicular lymphoma (FL)** account for approximately 65% of NHLs[1]; other major subtypes include chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL).[1,4] Non-Hodgkin lymphoma can also be categorized based on tumor grade. **Indolent lymphomas** (eg, FL and CLL/SLL) are slow growing and are often diagnosed at an advanced stage. Many patients with indolent lymphomas do not require treatment at the time of diagnosis, but those who do can be difficult to treat. In contrast, 60%–70% of aggressive lymphomas (eg, DLBCL) can be cured and require early therapy.[1,2]

Non-Hodgkin lymphoma accounts for about 4% of all new cancer cases in the United States, with the American Cancer Society estimating an incidence of 74,680 (both sexes) in 2018, leading to approximately 20,000 deaths, due to NHL this year.[5] Family history, lifestyle, certain viral and bacterial infections, and chemical exposures have all been linked to an increased risk for NHL.[1] Immunosuppression in patients following an organ transplant, or those treated for an autoimmune disorder, continues to be an important risk factor for NHL. Incidence of AIDS-related NHL has decreased in recent years, while cases in elderly patients have increased, with the number of patients aged 65 and older at the time of diagnosis increasing. The growing elderly population is becoming the largest cohort with FL.[5,6] Age, disease stage, performance status, and extranodal involvement are some of the clinical features that factor into prognosis.[7–11]

Presentation and Workup

A minority of patients present with constitutional symptoms, such as night sweats, fever, and unexplained weight loss, while most experience painless lymphadenopathy and symptoms related to local tumor growth. A definitive diagnosis is made by excisional biopsy of an enlarged lymph node that should be reviewed by an experienced hematopathologist.[2] Subtypes may be differentiated by histopathology, flow cytometry, and/or immunohistochemistry. Although molecular genetic profiling is not used routinely, it may be helpful in specific cases to identify chromosomal translocations associated with some subtypes.[2] PET or CT scans are useful for determining location and extent of disease (ie, staging), and bone-marrow

biopsy is recommended for identifying bone-marrow involvement, which is associated with increased risk of death in patients with high-grade lymphomas.[2,12]

Treatment of Aggressive NHL

According to the National Comprehensive Cancer Network (NCCN), the treatment algorithm for the most common forms of **aggressive** NHL (ie, DLBCL and FL grade 3b) is similar, consisting of chemoimmunotherapy regimens.[2] High-dose therapy and autologous stem-cell transplantation (HDT/ASCT) may be indicated in high-risk cases.[13] **Relapsed and refractory disease** is treated with standard chemoimmunotherapy, almost invariably followed by a referral to a hematopoietic stem cell transplantation center in view of undergoing HDT/ASCT.[2,14] In addition, novel agents such as anti-CD19 CAR T cells[15,16] were shown to induce responses in patients with relapsed and/or refractory DLBCL.[17]

Addition of the CD20 monoclonal antibody, rituximab, to chemotherapy, was a major advance in the treatment of NHL, which led to statistically and clinically significant improvements in progression-free survival (PFS), disease-free survival, and overall survival. The current standard of care is an anthracycline-based regimen, which includes rituximab (R) combined with cyclophosphamide (C), doxorubicin (H), vincristine (O), and prednisone (P), referred to as R-CHOP, administered every 3 weeks, and results in improved duration of remission compared with chemotherapy alone.[18,19] For the activated B-cell (ABC) subtype that is associated with poorer survival outcomes, more intensive regimens, such as DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab),[20,21] R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone),[22] or R-CHOP plus lenalidomide,[23] are also used. In frail and elderly (>70 years) patients with untreated DLBCL, a combination of bendamustine and rituximab (BR) demonstrated promising activity and manageable toxicity.[24]

For patients with MCL, R-CHOP, VR-CAP (R-CHOP in which bortezomib is used instead of vincristine),[25] BR,[26] or rituximab-hyperCVAD (rituximab in combination with fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with rituximab high-dose methotrexate/cytarabine) are used.[27] Most of these patients require a referral to a hematopoietic stem cell transplantation center. In the second line, Bruton's tyrosine kinase inhibitors (BTK), such as ibrutinib or acalabrutinib, were shown to have significant activity.[28]

First-line Treatment of Indolent NHL

For asymptomatic patients with low-grade FL, observation without initial therapy, ie, "watch and

wait," is still considered an appropriate approach.[29,30] The NCCN recommends treatment only for patients with FL meeting the *Groupe d'Etude des Lymphomes Folliculaires* (GELF) criteria—patients who have symptomatic, progressing, or bulky disease; if cytopenia or splenomegaly is present; or there is end-organ risk/damage.[2,31] Elderly, or patients with poor-performance, may be treated with a single agent, rituximab, often followed by maintenance rituximab, while more aggressive chemotherapy, such as BR, R-CHOP, R-CVP (cyclophosphamide, vincristine, prednisone), or radioimmunotherapy is available for patients who can tolerate it.[2] Recently, data presented at the American Society of Clinical Oncology 2018 meeting from the phase 3 RELEVANCE trial (NCT01650701; n=1030) showed a combination of rituximab and lenalidomide as a potential first-line chemo-free treatment option for patients with advanced, untreated, high-tumor-burden FL compared well to BR, R-CHOP, R-CVP (with a 3-year estimated interim PFS rate of 77% and 78%, respectively; 95% confidence interval = 0.85-1.43; *P* = .48), but with fewer side effects.[32] These findings suggest that rituximab-lenalidomide may be a reasonable option for patients who are not appropriate candidates for chemoimmunotherapy.

Second-Line treatment

For patients with relapsed FL, several treatments are available, such as newer anti-CD20 monoclonal antibody obinutuzumab, lenalidomide, small molecule tyrosine kinase inhibitors, bcl2 inhibitors, epigenetic modifiers, conjugated antibodies, and immune checkpoint inhibitors.[1,33] HDT/ASCT[34] and allogeneic-SCT[35] are sometimes used and can potentially result in a cure.

Advancing the Treatment Paradigm

The standard of care for indolent and aggressive NHL basically had been unchanged for more than a decade. However, advances in NHL have begun to accelerate with several new US Food and Drug Administration (FDA)-approved treatments, such as **copanlisib, acalabrutinib, obinutuzumab, and axicabtagene ciloleucel**.

Phosphatidylinositol 3-kinase (PI3K) is a protein that plays a critical role in activation, proliferation, and survival of B-cells. The FDA has approved 2 PI3K inhibitors, which target distinct isoforms of the PI3K enzyme, resulting in distinct toxicities and variable efficacy in the clinical setting.[36] There are 3 classes of the PI3K enzyme, with class I most commonly associated with malignancy. The class I PI3K enzyme is present in 4 general isoforms: α, β, γ, and δ. There are at least 3 mechanisms of action that account for the effectiveness of PI3K inhibitors: inhibition of signaling from the B-cell receptor, inhibition of

cytokine signaling from the microenvironment, and enhancement of antitumor immunity.[37] The PI3K inhibitors, in particular those targeting p110δ, are part of the new armamentarium against relapsed and refractory B-cell indolent NHL.[37]

Advances in Treatment—PI3K inhibitors

In 2014, the US FDA approved the first PI3K inhibitor, **idelalisib**, selective for the δ isoform. Idelalisib is an oral agent for the treatment of patients with relapsed FL in whom 2 prior lines of therapy have failed and in relapsed CLL/SLL in combination with rituximab. In the relapsed/refractory FL setting, this agent had an overall response rate of 57%, with a PFS of 11 months. In a pivotal phase 3 study (n=220), patients with relapsed CLL had an ORR of 81%, with a PFS of 93% at 24 weeks.[38] The most common grade 3 adverse events were neutropenia, transaminitis, diarrhea, and pneumonia. Although idelalisib efficacy is promising, high rates of toxicity—primarily in combination therapy with anti-CD20 antibodies—remain challenging, with serious gastrointestinal side effects that may limit its use.[36,37] Serious immune-mediated toxicities include colitis, hepatitis, and pneumonitis, which has resulted in an FDA-issued Boxed Warning with its approval. Monitoring and prophylaxis for pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) reactivation surveillance are recommended for patients taking idelalisib.[36]

The recently approved agent, **copanlisib**, is a pan-PI3K inhibitor, with preferential activity against p110α and p110δ isoforms.[37] It was approved in October 2017 for relapsed FL patients in whom 2 prior lines of therapy have failed, based on results of an open-label, nonrandomized phase 2 clinical trial (CHRONOS–1, NCT01660451).[37,39,40] Because of its unique pharmacokinetics, this intravenous monotherapy is administered once a week, for 3 weeks, followed by 1 week off. This agent has low rate of gastrointestinal side effects, as the IV medication largely bypasses the gastrointestinal tract. In CHRONOS-1, approximately 60% of patients responded, with 14% experiencing complete responses.[41] The most common serious adverse events (SAEs) include hyperglycemia and hypertension. Patients should be monitored for these adverse effects before and after each infusion. Because of these SAEs, copanlisib may not be the best option for patients with diabetes or hypertension. Other notable, but less frequent, side effects include declines in white blood cell counts and diarrhea/colitis.[39,40,42,43] It was also noted that side effects can cause treatment delays or dose reductions. With regard to additional settings, there are 3 ongoing randomized phase 3 trials exploring a potential use of copanlisib in indolent lymphomas. These include CRONOS-2 (copanlisib vs placebo in patients with rituximab-refractory disease;

NCT02369016), CHRONOS-3 (copanlisib in combination with rituximab vs placebo for relapsed disease; NCT02367040), and CHRONOS-4 (copanlisib in combination with standard chemoimmunotherapy (R-CHOP or B-R) vs standard chemoimmunotherapy alone for relapsed disease; NCT02626455), with the latter 2 actively recruiting.[44]

Duvelisib (formerly IPI-145) is a novel oral, dual-PI3K inhibitor, targeting p110δ and p110γ isoforms, with a similar mechanism of action to that of idelalisib. It recently completed its phase 3 DUO trial for relapsed/refractory CLL/SLL and indolent NHL.[43,45] The DUO study (NCT02004522; n=319) compared monotherapy duvelisib to ofatumumab in relapsed and refractory CLL/SLL. Duvelisib improved PFS by 3.4 months (hazard ratio [HR] 0.52; p = 0.0001) in the relapsed/refractory setting.[43,45] Results from the DUO study revealed a similar toxicity profile to idelalisib. The most severe AE (grade 3 or worse) were neutropenia (30%), diarrhea (15%), pneumonia (14%), anemia (13%), and colitis (12%). Five percent of participants discontinued the study due to diarrhea or colitis. Circa 1% of patients died from treatment-related AEs.[45] The FDA has accepted a new drug application (NDA) for duvelisib and granted it a priority review. The manufacturer is also seeking accelerated approval in relapsed/refractory FL, with anticipated action in October 2018.[45]

There are more than 50 ongoing clinical trials for emerging PI3K inhibitors, including umbralisib, RP-6530, and INCB050465.[37]

Other New Therapy Strategies for B-Cell NHL

Obinutuzumab is a type 2 anti-CD20 monoclonal antibody, approved in November 2017 for patients with previously untreated FL in combination with chemotherapy.[46] Results from the phase 3 GALLIUM trial (NCT01332968; n=1202) showed that obinutuzumab significantly prolonged PFS in patients with previously untreated, advanced-stage FL, compared to rituximab, when combined with CHOP, CVP, or bendamustine.[47] The primary endpoint of PFS was superior for obinutuzumab-based chemoimmunotherapy (PFS at 3 years, 80.0% vs. 73.3%).[47,48] Nonetheless, serious adverse events, such as infusion reactions and neutropenia, were more frequent in the obinutuzumab group than in the rituximab group (46.1% vs 39.9%). There was no overall survival (OS) benefit in any of the arms of GALLIUM trial. A total of 35 patients (5.8%) in the obinutuzumab group and 46 (7.7%) in the rituximab group died.[47] The combination of obinutuzumab-CHOP was associated with higher rates of ≥3-grade toxicity.[47] This drug is used intravenously in combination with chemotherapy, 1000 mg on days 1, 8, and 15 in the course of the first cycle. Obinutuzumab has also been FDA-approved as maintenance therapy, as it can reduce the risk of

relapse, allowing patients to stay in remission longer.[48,49] This being said, the concept of maintenance therapy with anti-CD20 antibodies has been embraced only by some clinicians, but not others, given the lack of OS benefit.

Axicabtagene ciloleucel (axi-cel), is an anti-CD19 chimeric antigen receptor (CAR) T-cell immunotherapy, initially developed at the National Cancer Institute, and commercially approved in October 2017 for patients with relapsed/refractory large B-cell lymphoma, including DLBCL arising from FL (also known as transformed FL).[50,51] This unique agent is manufactured from the patients' peripheral blood, during which T-cells are engineered to express a CAR that redirects them to recognize (and destroy) CD19-expressing cells.[51] The mechanism of action of axi-cel is unique—the decrease in tumor burden is not as rapid as cytoreductive therapy, but is sustained after a single-dose infusion.[51]

Approval of this novel agent was based on a single-arm, multicenter trial (NCT02348216; n=101) for patients with aggressive B-cell NHL. Patients in the ZUMA-1 phase 2 clinical trial received a single infusion of axi-cel, following completion of lympho-depleting chemotherapy. The objective response rate was 82%, with a complete response (CR) rate of 54% (95% CI: 41, 62). The median follow-up was 15.4 months, with ongoing responses in 42% patients, including 40% who had complete responses.[16] The most important acute toxicities include cytokine release syndrome (CRS), occurring in over 90% of patients (all grades), and neurologic events in 64% of patients (all grades). An important neurologic SAE, CAR T-cell-related encephalopathy syndrome (CRES) affects 34% of patients, with a median onset occurring at day 5 post infusion.[51] Close monitoring in specialized centers with expertise in this type of therapy is recommended with axi-cel. In the ZUMA-1 trial, tocilizumab (an anti-IL-6 monoclonal antibody) and high-dose corticosteroids were administered for the treatment of CRS and other neurotoxicity. This novel agent is seen as a promising treatment for patients with CD19-positive malignancies, including refractory DLBCL.

Conclusion

Tailoring therapy to individual patients, and their needs, is paramount in lymphoma. Thus, when deciding between approved PI3K inhibitors, side effects of these agents must be considered. Serious gastrointestinal side effects, including colitis and severe diarrhea, can be caused by the oral agent idelalisib. Copanlisib's IV administration helps bypass potential gastrointestinal toxicity issues. However, its SAEs include hyperglycemia and hypertension. Consequently, it may not be the best option for patients with diabetes or high blood pressure.[41]

Despite great progress, many NHL subtypes, including FL, remain incurable. Effective predictive biomarkers that would help treatment selection are still lacking. With regard to maintenance therapies, it is important to explain to patients that they will not cure the disease, but rather can help reduce the risk of relapse, allowing patients to stay in remission longer. In the long run, the availability of many effective agents for indolent lymphoma will improve survival, and perhaps lead to cure in some patients.

Clinical Case Scenario of a Patient with Indolent NHL

A 75-year-old woman with a history of lymphoma presented to her primary care physician with a painless right inguinal mass, and fatigue, for the previous 8 weeks. She denied fever, night sweats, or unintentional weight loss. Her oncology history included low-grade non-Hodgkin lymphoma stage IIA by Ann-Arbor staging system, diagnosed 10 years earlier. She had received therapy with rituximab, and entered a complete remission, without evidence of relapse to date. She also had well-controlled diabetes mellitus type 2, hypothyroidism, and uncomplicated hypertension. Home medications included glipizide, levothyroxine, hydrochlorothiazide, and atenolol. Family history was remarkable for lymphoma in her brother at age 65. She did not have significant history of tobacco, alcohol, or illicit drug use. The initial physical exam revealed axillary, inguinal, and iliac adenopathy with the largest size of 4 x 3 cm in the right groin and moderate pallor. Laboratory work-up showed a moderate normocytic anemia. A compete metabolic panel and lactate dehydrogenase were within normal range. The patient was admitted for further work-up.

Computerized tomography (CT) scan of abdomen and pelvis, with intravenous and oral contrast, followed by a positron emission tomography (PET)-CT scan, confirmed peripheral adenopathy, but also showed enlarged hypermetabolic mediastinal nodes and moderate uniform hypermetabolism in the spleen. An excisional biopsy of an axillary node was requested. Histologic, flow cytometric, and immunohistochemical findings were consistent with follicular lymphoma (FL) grade 2. A bone marrow aspiration and biopsy procedure for staging purposes showed 15% involvement with FL consistent with stage IVA disease. The patient received therapy with bendamustine-obinutuzumab for 6 cycles. She did not experience any significant infusion reactions. During the outpatient follow-up, the patient reported significant improvement in fatigue. A PET-CT scan after 3 cycles showed resolution of metabolic activity at all disease sites. As she developed a low white-blood-cell count, she required growth factor support with each cycle in anticipation of febrile neutropenia. Her anemia improved and resolved completely 10 weeks after completion of chemoimmunotherapy. She was then started on maintenance therapy with obinutuzumab.

Eighteen months later, the patient noticed an enlarging right neck node. She had no evidence of fever, night sweats, or weight loss. An excisional biopsy showed relapsed FL grade 2. A PET-CT showed only right lower neck and mediastinal adenopathies. A bone-marrow aspiration and biopsy showed no involvement with lymphoma. Options for therapy were discussed with the patient.

Given her history of diabetes and hypertension, the choice of therapy was idelalisib. The patient was made aware of idelalisib's adverse events, such as neutropenia, transaminitis, diarrhea, and pneumonia. She asked pertinent questions about the serious toxicities of idelalisib, such as colitis, hepatitis, and pneumonitis. She was offered PJP prophylaxis. She responded promptly to idelalisib, with resolution of all adenopathies within 12 weeks, and only minimal transaminitis that did not require dose reductions.

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