

Addressing the Challenges of Aggressive Lymphomas

PRESENTED BY KATHERINE L. BYAR, MSN, ANP-BC, BMTCN®, and MATTHEW LUNNING, DO, FACP

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From the Fred & Pamela Buffett Cancer Center, Omaha, Nebraska

Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Katherine L. Byar, MSN, ANP-BC, BMTCN®, and Matthew Lunning, DO, FACP, covered how to tackle challenges in the treatment of aggressive lymphomas by understanding how to apply emerging data, reviewing optimal therapies and treatment recommendations, and discovering how to manage associated adverse events in this disease state at JADPRO Live 2019.

With an estimated 74,200 new cases in 2019, non-Hodgkin lymphoma (NHL) ranks seventh among men and women as the most frequently newly diagnosed cancer in the United States (American Cancer Society, 2019). Although death from this heterogeneous group of neoplasms is in decline due to improved treatments, approximately 20,000 people will die from NHL in 2019.

At JADPRO Live 2019, Katherine L. Byar, MSN, ANP-BC, BMTCN®, and Matthew Lunning, DO, FACP, of the Fred & Pamela Buffett Cancer Center in Omaha, Nebraska, discussed the clinical significance of emerging data regarding the management of aggressive lymphomas, selecting optimal therapy for patients with aggressive lymphomas, and managing adverse events.

INDOLENT VS. AGGRESSIVE LYMPHOMA

As Ms. Byar explained, there are more than 60 different subtypes of NHL, and each has its own pattern of growth and response to treatment. The best way to categorize these lymphomas is indolent (low grade) vs. aggressive (intermediate/high grade). Indolent lymphomas are characterized by slow disease progression and frequently asymptomatic progression. Patients with indolent disease may not need treatment for years and typically have a high response rate to first-line treatment regimens.

“Unfortunately, approximately 70% of indolent patients are diagnosed with stage 3 or 4 disease,” said Ms. Byar. “Invariably, these patients will relapse, and they have lower response rates and shorter duration of response after each relapse.”

Indolent lymphoma is felt to be incurable with standard therapy

and ultimately has a continuous risk of transformation to aggressive lymphoma, which is characterized by aggressive progression of disease. Aggressive lymphomas are usually more sensitive to chemotherapy, said Ms. Byar, who noted that 30% to 60% of patients can be cured. Most relapses occur within the first 2 years of treatment, and one third of patients at diagnosis have B symptoms of fevers, night sweats, and weight loss (Table 1).

FIRST-LINE STANDARD OF CARE FOR DLBCL

As Dr. Lunning reported, the first-line therapy for diffuse large B-cell lymphoma (DLBCL) has been the standard of care for many decades: R-CHOP, a chemotherapy combination of rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone. For stage 1 or 2 non-bulky disease (< 7.5 cm), treatment is R-CHOP for three to four cycles with radiotherapy or R-CHOP for six cycles with or without radiotherapy. For bulky disease (≥ 7.5 cm), treatment is R-CHOP for six cycles with or without radiotherapy. In stage 3 or 4 disease, the standard of care is R-CHOP for six cycles with or without radiotherapy.

“While there have been many recent challengers to R-CHOP in front-line DLBCL, there has been no change in therapy, even in patients with germinal center B-cell (GCB) and activated B-cell (ABC) subtypes,” said Dr. Lunning.

PERIPHERAL T-CELL LYMPHOMAS

While B-cell lymphomas represent about 90% of all newly diagnosed NHL, peripheral T-cell lymphomas (PTCLs) represent the other 10%. As Dr. Lunning explained, PTCLs are very tricky to diagnose, often requiring many days after biopsy for a diagnosis to be rendered, or repeat biopsy may be necessary. Moreover, these diseases have been associated with poor prognosis, but the best performing subtype is *ALK*-positive anaplastic large cell lymphoma.

ECHELON-2, a double-blind trial, randomized patients to either brentuximab vedotin plus chemotherapy regimen brentuximab vedotin + CHP or the chemotherapy regimen CHOP, and was the largest study to date in PTCL (Horwitz et al., 2019). The primary endpoint was progression-free survival, said Dr. Lunning, and 75% of patients had anaplastic large cell lymphoma, while 25% had PTCLs that expressed at least 10% CD30. Results showed an overall survival advantaged for brentuximab vedotin + CHP.

Ms. Byar cautioned against the appearance of peripheral neuropathy, infusion reactions, neutropenia, tumor lysis syndrome, and Stevens-Johnson syndrome. The most common adverse events with brentuximab vedotin are anemia, cough, diarrhea, fatigue, nausea, neutropenia, peripheral neuropathy (sensory), pyrexia, rash, thrombocytopenia, upper respiratory infection, and vomiting.

Table 1. Indolent vs. Aggressive Lymphomas

Indolent (low grade)	Aggressive (intermediate/high grade)
<ul style="list-style-type: none"> Follicular (grade 1-2), SLL/CLL, MZL, LPL, MCL, grade 3A FL Slow disease progression 70% present with stage III or IV disease May not need treatment for years High response rate to first treatment regimens Invariably will relapse After relapse, lower response rates, shorter duration of response Felt to be incurable to standard therapy Transform to aggressive lymphoma Presentation: often asymptomatic 	<ul style="list-style-type: none"> DLBCL, most T cells, MCL: FL, FL grade 3B, TCL, FL grade 3A Burkitt, lymphoblastic, high grade Aggressive progression of disease 50% present with stage III or IV disease Usually more sensitive to chemotherapy Higher response rates if treated 30%-60% of patients can be cured Most relapses occur within first 2 years 1/3 have B symptoms Presentation: symptomatic

Note. SLL/CLL = small lymphocytic lymphoma/chronic lymphocytic leukemia; MZL = marginal zone lymphoma; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; TCL = T-cell lymphoma. Information from Swerdlow et al. (2016).

EMERGING AGENTS FOR R/R AGGRESSIVE B-CELL NHL

R-CHOP remains a standard of care for aggressive B-cell lymphoma, but other novel therapies such as antibody-drug conjugates and immunomodulators have shown promise for relapsed or refractory disease. The addition of polatuzumab vedotin to bendamustine and rituximab showed an overall survival advantage vs. bendamustine and rituximab alone and led to its approval by the U.S. Food & Drug Administration (FDA) as a combination therapy in relapsed/refractory DLBCLs that have had at least two prior therapies (Sehn et al., 2019).

As Ms. Byar explained, peripheral neuropathy and infusion reactions are dose-limiting factors, and the latter are more common with polatuzumab vedotin than brentuximab vedotin.

In patients with ABC subtype in the relapsed/refractory setting, said Dr. Lunning, the use of lenalidomide and rituximab has also generated some response, but the durability of this regimen is still in question (Wang et al., 2013). Although there is a complete remission rate of approximately 22%, median progression-free survival is only 3.7 months, Dr. Lunning added.

Ms. Byar noted that lenalidomide is associated with rashes and mild gastrointestinal toxicities such as diarrhea or nausea.

“The best way to handle gastrointestinal side effects is to administer lenalidomide at night,” said Ms. Byar, who noted that watching blood counts for myelosuppression is also important.

CAR T-CELL THERAPY

As Dr. Lunning reported, chimeric antigen receptor (CAR) T-cell therapy has also generated a lot of excitement for the treatment of hematologic malignancies. The technology involves capturing a patient’s autologous T cells, shipping them off to a manufacturing location, and inserting a CAR gene via retroviral vector into the patient’s T cells. Because it is expressed on the surface of most B-cell malignancies, but its expression is restricted to B cells and their precursors, CD19 is an ideal target. There are currently two FDA-approved constructs, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, and a third, liso-cel, that is in late development.

As Dr. Lunning explained, axi-cel, which has a CD28 co-stimulatory molecule, was tested in the

ZUMA 1 trial (n = 101) with a median follow-up of more than 2 years. The best overall response rate was 83%, with a 58% complete response rate (Locke et al., 2019).

“Results showed complete responses in patients who were double refractory, and it appears the CAR T cells were agnostic to poor prognostic genetic factors, like double-hit lymphomas and double-expressing lymphomas,” said Dr. Lunning, who noted that the duration of response was approximately 11.1 months, and the median progression-free survival was 5.9 months. “What’s generated excitement, however, is that at 2 years, 39% of patients are progression-free.”

The second construct, tisagenlecleucel, uses a 4-1BB co-stimulatory molecule. A study of 93 patients with a median follow-up of 14 months demonstrated a best overall response rate of 52%, with a complete response rate of 40% (Schuster et al., 2019).

“Both younger and older patients had responses,” said Dr. Lunning, who noted that at the 12-month response period, 65% of patients who achieved a response were relapse free, and 79% who achieved a response remained in complete response. “These are encouraging data.”

While axi-cel and tisagenlecleucel were approved for relapsed/refractory DLBCL, the final construct, liso-cel, expanded the enrollment population. The TRANSCEND trial looked at people in the core group of DLBCL, not otherwise specified, transformed follicular lymphoma, and high-grade B cell lymphomas, which were double hits and triple hits. As Dr. Lunning reported, liso-cel, which also uses a co-stimulatory 4-1BB molecule, has a different manufacturing process involving individually formulated CD4 and CD8 suspensions through lentiviral transduction.

In 38 patients, data from the TRANSCEND trial showed a best overall response rate of 80%, with a complete response rate of 50%, and 50% of those patients remain in complete response at 6 months (Abramson, 2019).

“Across three constructs, we’re seeing activity in patients who are heavily refractory to chemotherapies, and we are potentially seeing some signs of durability in those patients who achieved complete response at about 3 months,” said Dr. Lunning.

CAR T-Cell Toxicities and Multidisciplinary Care

As Ms. Byar reported, despite the impressive response rates in heavily pretreated patients, CAR T-cell therapy is associated with significant toxicities, including cytokine release syndrome (CRS) and neurotoxicity. In the axi-cel trial, CRS occurred in 93% of patients and 64% of patients had neurotoxicity. Because of these toxicities, said Ms. Byar, CAR T-cell products should be dispensed and administered in a health-care facility that is enrolled and compliant with Risk Evaluation and Mitigation Strategy (REMS) programs (Figure 1).

“CRS and neurological toxicities or immune effector cell-associated neurotoxicity syndrome can be life-threatening, which is why it’s necessary to adhere to REMS guidelines as well as the manufacturing guidelines for each of these CAR T-cell therapies because they are so different,” said Ms. Byar.

According to Ms. Byar, close collaboration with a multidisciplinary team is also essential for positive patient outcomes and successful implementation of this therapy, and advanced practitioners, in particular, play a vital role in the manage-

ment of adverse events associated with these new novel agents.

“Prompt recognition of CRS and neurological events post CAR T-cell therapy are crucial,” said Ms. Byar. “One of the things you might consider is having your patient shake your hand to identify a tremor that might be indicative of neurotoxicity.” ●

Disclosure

Dr. Lunning has received research support from Amgen, BMS, Celgene, Curis, Juno, Janssen, Pharmacyclics, and TG Therapeutics, and has consulted for AbbVie/Pharmacyclics, Bayer, Cardinal Healthy, Celgene/Juno, Dava, Janssen, Gilead/Kite, Novartis, Portola, Seattle Genetics, Spectrum, TG Therapeutics, Vanium, and Verastem. Ms. Byar has no conflicts of interest to disclose.

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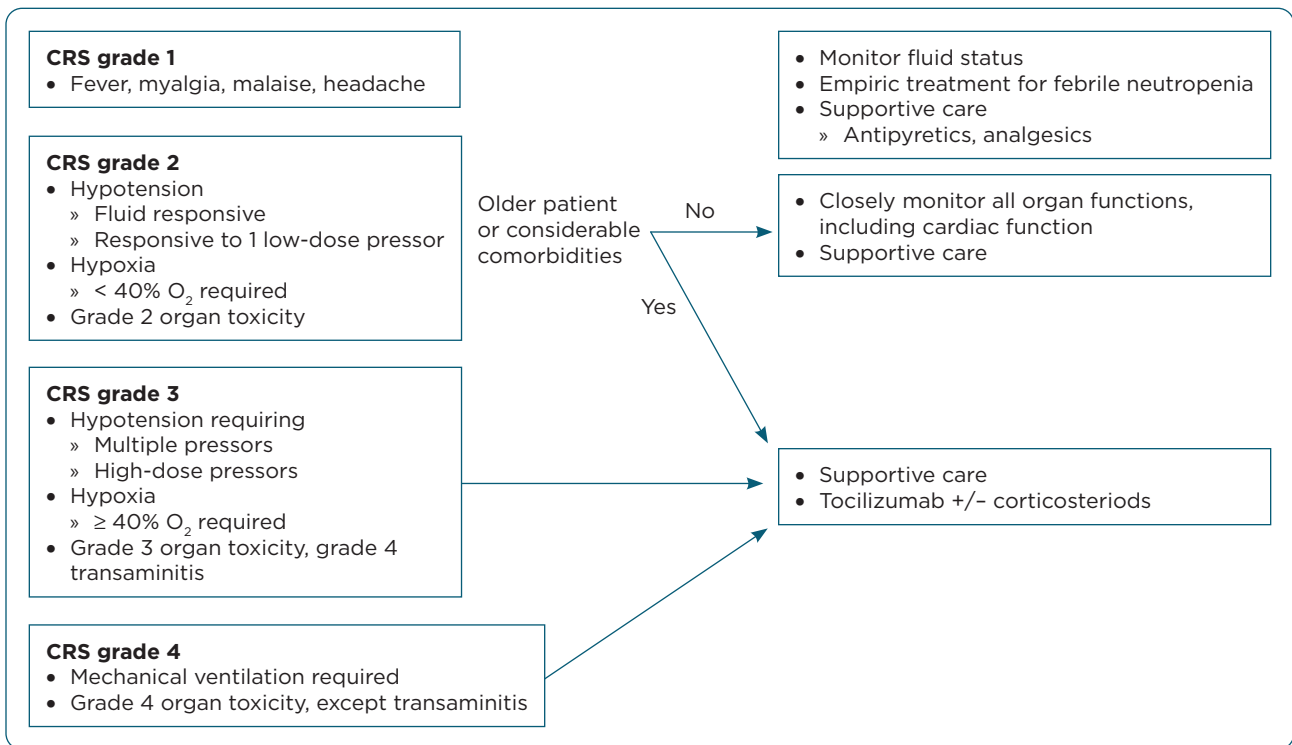


Figure 1. Post-infusion cytokine release syndrome management. Information from Adkins (2019); Riegler et al. (2019).

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