ABSTRACT

The development of brentuximab vedotin, nivolumab, and pembrolizumab has revolutionized the treatment of classical Hodgkin lymphoma. Continuous efforts are underway to improve the established early-line treatment regimens, incorporating these novel systemic therapies as either replacements for or additions to conventional agents. Although brentuximab vedotin, nivolumab, and pembrolizumab have demonstrated efficacy both as monotherapies and in combinations, critical questions remain regarding the sequencing of these agents, as well as the role of radiation therapy and interim PET scans.

“**In the last 10 years,** there have been quite a few advances [in the treatment of classical Hodgkin lymphoma], and the stage has been set with FDA approvals for 3 novel drugs: brentuximab vedotin, nivolumab, and pembrolizumab,” commented Ryan C. Lynch, MD, Associate Professor, Fred Hutchinson Cancer Center, and the University of Washington School of Medicine, and member of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Panel for Hodgkin Lymphoma (HL). He discussed the emerging systemic therapy options that are changing the early-line treatment paradigm, as well as the appropriate settings for the use of immune checkpoint inhibitors, at the NCCN 2023 Annual Congress: Hematologic Malignancies.

Advances in Classical HL Management

“It has been very busy … in the HL field,” Dr. Lynch remarked. Although brentuximab vedotin, nivolumab, and pembrolizumab were initially approved as monotherapies in the relapsed setting, he emphasized, “We have learned a lot … about how to utilize these drugs, how to sequence them, and how to combine them.”

Dr. Lynch also commented on the widespread adoption of PET scans approximately 20 years ago, highlighting their potential for accurate staging and response assessment. “[This], therefore, allowed therapy to be tailored to the individual patient, and radiation fields to be more limited.”

The PET-Adapted Era

A prospective study “set the stage for the next decade of HL studies …, looking at how therapy can be adapted based on interim PET [results],” according to Dr. Lynch. He explained that the prognostic value of the scans conducted after 2 cycles of therapy (PET2) was found to surpass that of the International Prognostic Score.

In the RAPID trial, patients with early-stage classical HL without bulky disease and who achieved PET negativity after undergoing 3 cycles of chemotherapy with doxorubicin + bleomycin/vinblastine/dacarbazine (ABVD) without radiation therapy (RT) seemed to experience a similar progression-free survival (PFS) compared with those who received consolidative RT.1 “This has been adopted into the NCCN Guidelines,” commented Dr. Lynch.

The discourse subsequently shifted to the RATHL trial,2 which evaluated the efficacy of PET-adapted therapy in patients with stage II or advanced-stage disease. After undergoing induction therapy with ABVD, he explained, those with negative PET2 results were randomly assigned to either continue this chemotherapeutic regimen or omit bleomycin; patients with PET2-positive results received bleomycin + etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone (BEACOPP)—based therapy.

“[In the PET2-negative arm, the 3-year PFS was] just outside of its predetermined noninferiority margin,” Dr. Lynch remarked. “[Despite this, doxorubicin + vinblastine/ dacarbazine (AVD)] has been integrated into the NCCN Guidelines as an option [in this clinical context].”

In patients with PET2-positive disease, the 3-year PFS rate was 67.5%.2 He pointed out that this represented an improvement compared with historical control data.

Limitations of PET-Adapted Therapy

The post hoc analysis of the aforementioned RAPID trial was conducted to determine whether the maximum tumor dimension may impact outcomes.3 According to Dr. Lynch, compared with patients who had a tumor dimension ≥5 cm
and underwent RT, those treated without such an intervention experienced worse event-free survival outcomes.

“[These data] open a discussion with patients in regard to abbreviated chemotherapy and no RT,” he remarked. “This was further illustrated in the EORTC H10 study, which was stopped early due to increased disease progression events in the RT-free arm.”

Dr. Lynch noted that the 5-year follow-up of SWOG S0816, a trial sharing a similar design with the RATHL study, further highlighted the limitations of PET-adapted therapy. “Over time, there were more [disease] progression events than would’ve been expected based on the initial analysis; the difference in PFS between those who received ABVD [versus] BEACOPP was only 10%,” he explained. “This illustrates that interim PET [results are] not a perfect surrogate marker of long-term outcomes in this population.”

**Moving Novel Agents Into Earlier Lines of Treatment**

“Good outcomes in the relapsed setting and in combination...will move [some of these novel agents] into earlier lines of treatment,” Dr. Lynch commented. “Moving these novel agents earlier in treatment has improved outcomes in patients with HL.” However, the potential effect on the aforementioned PET-adapted paradigms has complicated the picture.

The ECHELON-1 trial revealed higher rates of toxicity but improved PFS with brentuximab vedotin-containing versus bleomycin-containing chemotherapy in previously untreated patients with advanced-stage disease, thus supporting the substitution of this CD30-directed antibody–drug conjugate in experimental first-line regimens. He stated that this population derived a PFS benefit with brentuximab vedotin + AVD (BV-AVD) versus ABVD that was “maintained and expanded with longer follow-up.” The estimated 6-year PFS rates were 82.3% and 74.5% with BV-AVD and ABVD, respectively.

“Additionally, this last year, [ECHELON-1 was] one of the very few studies in the untreated setting to demonstrate an overall survival benefit,” Dr. Lynch remarked. “BV-AVD has been integrated into the NCCN Guidelines, and it also received FDA approval [in this clinical context] a number of years ago.”

Based on a 5-year follow-up analysis, which stratified patients by interim PET result, Dr. Lynch concluded: “Interim PET [scans are] helpful, but with BV-AVD [they] may not be as helpful because more [PET-positive] patients are still cured than not.” He further emphasized the need for better surrogate endpoints.

ECHELON-1 gave rise to the next generation of studies, namely, KEYNOTE-204, which demonstrated the PFS superiority of pembrolizumab over brentuximab vedotin in the relapsed setting. “[This PD-1 inhibitor] now has an FDA label for second-line therapy onward,” commented Dr. Lynch.

Considering these data, questions were posed regarding whether PD-1 inhibitors may outperform brentuximab vedotin in combination with chemotherapy in untreated patients. The SWOG S1826 trial seemed to confirm this hypothesis; based on an interim analysis, patients with advanced-stage disease who were treated with nivolumab + AVD (N-AVD) demonstrated a higher 1-year PFS rate than those who received BV-AVD (94% vs 86%, respectively; P=.0005). Despite these “promising” results, according to Dr. Lynch, longer-term follow-up data are needed before this regimen may be considered for integration into the NCCN Guidelines.

“Notably, there is more neutropenia with N-AVD,” he added. “Growth factors were not required, but they were required with BV-AVD; so, this explains some of that.”

**Questions for the Future**

Dr. Lynch concluded by presenting the key questions being explored in the field of HL. For previously untreated patients with early-stage disease and who are receiving a novel agent combination followed by RT, he stated: “[The NIVAHL and BREACH trials have yielded] remarkable outcomes,” raising the question of whether RT is necessary in this clinical context. An updated follow-up analysis of a study addressing this issue is scheduled for presentation at the 2023 American Society of Hematology (ASH) Annual Meeting & Exposition.

Based on the previously discussed results of the 5-year follow-up analysis of the ECHELON-1 trial, Dr. Lynch again questioned the continuously “challenging” role of interim PET results in treatment decision-making for patients who have received a novel agent combination. He commented, “If I know patients are responding to brentuximab vedotin, I probably wouldn’t order a PET [scan], because if it is positive, it will create a lot of anxiety for them, even though they have a better chance of being cured than not.”

Taking this question one step further, Dr. Lynch thinks “Having some noninvasive tools that are not susceptible to false-positives would be very helpful.” One potential approach involves the assessment of circulating-tumor DNA (ctDNA) clearance, which was found to be associated with superior PFS outcomes when measured after the second cycle and on completion of treatment with chemotherapy plus a PD-1 inhibitor.

“Despite not having all clean PET [scans] at the end, over time, [the percentage of ctDNA clearance has] reassured us that these patients really haven’t relapsed,” Dr. Lynch commented. “If these tools become widely available, this is something that will help us to improve outcomes in both HL and non-HL.”
Figure 1. Selected new classical Hodgkin lymphoma agents in clinical trials.

As the discourse moved toward the potential role of genotype-based risk stratification, he explained that genetic subtypes of classical HL fall into 2 dominant categories: mutations that affect NF-κB/STAT/PI3K signaling (H1), and genomic instability mediated through p53-mutated and Epstein-Barr Virus–driven disease (H2). Despite the analysis having focused on a mixed group of patients treated with different regimens, significantly superior clinical outcomes were observed in those with the H1 versus H2 subtype.14

“There are ongoing clinical trials in HL,” Dr. Lynch concluded. “No drugs are going to get approved right away, but newer promising agents are just entering clinical trials (Figure 1).

References