Managing Relapsed Disease in Peripheral T-Cell Lymphoma: Highlights From SOHO 2020

Outcomes for relapsed peripheral T-cell lymphoma (PTCL) have been largely defined by the utility of stem cell transplant, wherein retrospective analyses illustrate relatively limited benefit from autologous transplant (Horwitz et al., 2005; Zeleertz et al., 2003). Allogeneic transplant, on the other hand, offers both progression-free survival and overall survival advantages. There is, however, a significant risk of transplant-related mortality that makes this treatment option reasonable for only a highly select subset of relapsed PTCL patients (Goldberg et al., 2012; Mehta-Shah et al., 2017).

**CHEMOTHERAPY**

Nontransplant treatment options include either single-agent or combination chemotherapy. A review of outcomes from the COMPLETE registry of relapsed PTCL patients supports the preference of single-agent options in second and later lines of therapy due to the progression-free survival advantage compared with more aggressive combination therapy approaches (Lunning, Moskowitz, & Horwitz, 2013; Stuver et al., 2019). Nevertheless, benefits seen with pralatrexate (Folotyn), romidepsin (Istodax), and belinostat (Beleodaq) are modest at best, with response rates around 25% to 30% and a median progression-free survival of around 2 to 4 months for each of these agents (Coiffier et al., 2012; O’Connor et al., 2011; O’Connor et al., 2015). Brentuximab vedotin (Adcetris) has been more of a standout, especially in anaplastic large cell lymphoma (ALCL) where CD30 is almost universally expressed (Horwitz et al., 2014; Pro et al., 2012). These generally poor outcomes have led investigators to target specific disease features such as activating mutations in the JAK/STAT pathway and overexpression of GATA3.

**JAK INHIBITORS**

A third of patients with certain subtypes of PTCL harbor activating mutations in the JAK/STAT pathway (Crescenzo et al., 2015; Jerez et al., 2012; Kiel et al., 2014; Kiel et al., 2015; Koskela et al., 2012; Küçük et al., 2015). A phase II study designed by Dr. Alison Moskowitz at Memorial Sloan Kettering Cancer Center sought to evaluate the use of the JAK1/2 inhibitor ruxolitinib (Jakafi) in patients with relapsed PTCL and stratified patients into three cohorts: those with an activating JAK/STAT mutation, those with functional evidence of JAK/STAT activation via elevated STAT3 or STAT5 by immunohistochemistry, and those not meeting either of these cri-
teria (Moskowitz et al., 2019). All patients took ruxolitinib 20 mg by mouth twice daily. Responses in the cohorts relying on the JAK/STAT pathway as a driver had overall response rates close to 30% (similar to available options). This study also revealed that pS6 expression may be predictive of response to ruxolitinib.

**Key Points**
- There have been historically poor response rates in patients with relapsed PTCL receiving single-agent chemotherapies, although brentuximab vedotin has produced improved response rates.
- New therapies targeting activating mutations in the JAK/STAT pathway and overexpression of GATA3 are being investigated.
- Advanced practitioners should be on the alert for immune-mediated toxicities and risk of infection in patients taking PI3K inhibitors.

**PI3K INHIBITORS**
Overexpression of GATA3 in PTCLs has been noted to respond to PI3K inhibition (Iqbal et al., 2014). Duvelisib (Copiktra) is a dual phosphoinositide 3 kinase (PI3K) inhibitor targeting the δ and γ PI3K isoforms. The ongoing phase II PRIMO study was preceded with a dose optimization lead-in comparing duvelisib 25 mg or 75 mg by mouth twice daily (Horwitz et al., 2019). In this phase, patients assigned to the higher dose had higher overall response (54% vs. 35% for 75-mg and 25-mg cohorts, respectively) and complete response rates (31% vs. 25%, respectively) by investigator assessment and a notably longer duration of response (12 months vs. 3 months, respectively). Expansion of this study has patients taking duvelisib at 75 mg by mouth twice daily for 2 months followed by a planned reduction to 25 mg by mouth twice daily thereafter in responding patients. Rapid disease control appears to have downstream impact on the depth and duration of response since a number of patients in the lower dose of the lead-in did not make it that far on treatment before progressing. Given the promise of this approach, novel combinations with duvelisib and either bortezomib (Velcade) or romidepsin are already being evaluated; early results with impressive response rates were seen with the addition of romidepsin (55% overall response rate, 31% complete response across subtypes), especially when looking at patients with angioimmunoblastic T-cell lymphoma/T-follicular helper subtype (Horwitz et al., 2018).

**OTHER AGENTS**
While ruxolitinib and duvelisib represent two investigational agents in relapsed PTCL, other attractive agents/pathways include epigenetic modifiers, monoclonal antibodies (e.g., mogamulizumab, antibody-drug conjugates), EZH1/2 inhibitors, and targeting the CD47 “don’t eat me” signal on tumor cells. In fact, epigenetic modifiers (hypomethylating therapy or histone deacyelase inhibitors) are also being combined with cyclophosphamide, doxorubicin, vincristine (Onocvin), and prednisone (CHOP) chemotherapy in the frontline setting (NCT03542266). Chimeric antigen receptor (CAR) approaches with T cells, or even NK cells due to the concerns for fratricide and T-cell aplasia, are of interest for the management of relapsed PTCL (Scarfò et al., 2019).

**The Advanced Practitioner Perspective**
Current research into the management of relapsed PTCL focuses on improving rates and durability of response. An inherent challenge facing researchers in this field is the heterogeneity across subtypes of PTCL and relative infrequency of some of these lymphomas. Advanced practitioners play a major role in implementing these treatments where appropriate.

Some providers may already have experience using some of these potential new options and can counsel and manage patients on agents like ruxolitinib or duvelisib. However, if the approach taken in the PRIMO study were to lead to incorporation of duvelisib into the treatment paradigm, providers should recognize the unique aggressive up-front dosing, which may complicate prescribing and lead to tolerability hurdles. Recognition of immune-mediated toxicities such as rash, colitis, hepatitis, and even pneumonitis is extremely important when caring for patients on duvelisib. Also, it is important to remember the need for anti-infective prophylaxis, including for the opportunistic infection Pneumocystis jirovecii pneumonia and ongoing monitoring for cytomegalovirus reactivation.

**Disclosure**
Dr. Valla has no conflicts of interest to disclose.
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