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LYMPHOID NEOPLASIA

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Dual PI3K blockade: PTCL's Achilles heel?

Jonathan E. Brammer | The Ohio State University James Comprehensive Cancer Center

In this issue of *Blood*, 2 companion articles by Flinn et al[1] and Horwitz et al[2] present promising phase 1 data demonstrating clinical efficacy of the dual inhibitor of phosphatidylinositol 3-kinase (PI3K)-δ and PI3K-γ duvelisib in patients with advanced hematologic malignancies, including T-cell lymphomas (TCLs).

The novelty of the therapeutic approach described in these reports lies with the dual inhibition of both PI3K-δ and PI3K-γ by duvelisib. PI3K-δ activation results in increased proliferation and growth of malignant B-cell leukemia and lymphoma cells.[3] Alternatively, PI3K-γ activation is associated with increased stability in the tumor microenvironment, through induction of immune-suppressive M2 tumor-associated macrophages, which mediate subsequent immune suppression and decrease in $CD8^+$ cytotoxic T-lymphocyte activation.[4] The hypothesis is that dual inhibition of both the PI3K-δ and PI3K-γ isoforms in malignant cells will produce increased cytotoxicity and, therefore, clinical responses in patients with a broad range of hematologic malignancies.

In the report by Flinn et al, the authors report on a phase 1, open-label study in 210 patients with a broad range of relapsed/refractory hematologic malignancies, including indolent non-Hodgkin lymphomas (iNHL), chronic lymphocytic leukemia (CLL), TCLs, and other hematologic malignancies. The trial included both a dose-escalation phase of 31 patients and an expansion phase of 179 patients. Patients were treated with twice-daily oral duvelisib for 28-day cycles until progression, intolerance, or discontinuation by patient or physician choice. The maximum tolerated dose of duvelisib was determined to be 75 mg twice daily. However, pharmacodynamic testing of phospho-AKT (pAKT), a key mediator in PI3K signaling, in CLL cells and patient samples demonstrated maximal inhibition of pAKT at the 25-mg dose without an increase in inhibition at higher levels of the drug. Therefore, the dose of 25 mg was selected for the dose-expansion cohort and future prospective studies. Grade 3 adverse events included neutropenia (32%), alanine transaminase/aspartate aminotransferase increase (20% and 15% respectively), anemia/thrombocytopenia (15% each), diarrhea (11%), and pneumonia (10%). The overall response rate (ORR) was assessed by the local investigator and was 58% in iNHL, 50% in peripheral TCL (PTCL), 32% in cutaneous TCL (CTCL), and 56% in relapsed/refractory CLL. The median time to response was 1.8 months.

Given the significant response of TCLs to duvelisib in the phase 1 trial, the second report by Horwitz et al further investigated the activity of duvelisib in TCL. The authors first evaluated clinical outcomes in the subset of patients with both PTCL and CTCL. Thirty-five patients with TCL in total were treated (16 with PTCL and 19 with CTCL). The ORR was 50% in PTCL (3 complete responses and 5 partial responses) and 31.6% in CTCL (6 partial responses), although absolute numbers were low. This rate of response is unexpected among TCL patients given the aggressive nature of these lymphomas.

Next, the authors evaluated the mechanism of action of duvelisib by studying in vitro and in vivo models of TCL with both cell lines and a patient-derived xenograft (PDX) mouse model. Duvelisib was tested in 11 PTCL lines in vitro. Cytotoxicity was observed in 3 of 4 cells lines with constitutively active pAKT. However, 0 of 7 lines without active pAKT demonstrated cytotoxicity, suggesting pAKT could be used as a predictive biomarker in future investigations. Interestingly, the authors tested one of these resistant cell lines with duvelisib in combination with the histone deacetylase inhibitor (HDACi) romidepsin, which is approved for the treatment of TCLs. Synergistic activity was noted with this combination, which suggests that further understanding of the pathogenesis of the PI3K pathway in TCL may lead to greater understanding of TCLs and other possible therapeutic combinations with duvelisib. Utilizing a phosphoproteomic approach (P100) and immunoblotting, the authors demonstrated that duvelisib treatment resulted in dose and time-dependent G1 cell cycle arrest with a concomitant reduction in cyclin D1. Furthermore, in the PDX mouse model utilizing an angioimmunoblastic TCL xenograft, duvelisib resulted in spleen shrinkage and induction of tumor-associated macrophages from an M2 immune-suppressive phenotype to an M1 inflammatory phenotype. These findings support the notion that duvelisib acts through the 2 primary mechanisms of PI3K-δ *and* PI3K-γ blockade in TCLs. First, duvelisib induces cell cycle arrest in G1 phase, with subsequent cell death. Second, inhibition of PI3K-γ stimulates M1 (immune-activating) macrophages in the microenvironment while inhibiting protumor (immune-suppressive) macrophages.

The finding that duvelisib is active in relapsed/refractory TCL is of particular interest to the field. PTCL is a particularly

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aggressive subset of lymphoma, with long-term cure rates of ~35%.[5] In patients with relapsed/refractory PTCL, few treatment options are available. Response rates with US Food and Drug Administration–approved therapies in PTCL are low. The HDACi's romidepsin and belinostat have ORRs of 25% and 29%, respectively, whereas the folate antagonist pralatrexate has an ORR of 29%.[6-9] The only exception is anaplastic large cell lymphoma, which universally expresses CD30, which is an exquisite target for the CD30 drug–antibody conjugate brentuximab vedotin. In the relapsed refractory setting, ORR with brentuximab vedotin approaches 80%.[10] In CTCL, while the course of the disease is often more indolent, once the pace of the disease accelerates, remissions are short, there is high morbidity, and the disease can transform to a more aggressive and eventually fatal subtype. Novel therapeutics are critically needed in relapsed/refractory TCLs. To date, PI3K inhibitors such as the PI3K-δ inhibitor idelalisib have not demonstrated clinical success in TCLs and have limited efficacy in CLL and iNHL. Although the number of TCL patients treated with duvelisib in these studies is relatively low, these results suggest a new therapeutic approach for patients with these rare diseases. This is particularly important given recent investigations that suggest that PD-1 blockade may paradoxically lead to progression in TCLs.[11,12] Prospective studies with central review of clinical responses in larger populations of patients are needed to conclusively evaluate the role of duvelisib in TCLs and other lymphoma subtypes.

These 2 studies demonstrate that dual inhibition of both PI3K-δ and PI3K-γ induces clinically meaningful antitumor responses, even in relapsed/refractory hematologic malignancies. Furthermore, these effects are seen in multiple diseases, including TCLs. Phase 2 clinical trials are underway with duvelisib in CLL and iNHL, with one currently planned in TCLs. These results will ultimately demonstrate whether dual inhibition of this critical pathway can impact clinical outcomes.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Aschemeyer et al, page 899

How does hepcidin hinder ferroportin activity?

De-Liang Zhang and Tracey A. Rouault | Eunice Kennedy Shriver National Institute of Child Health and Human Development

In this issue of *Blood*, Aschemeyer et al found that hepcidin bound to the central cavity of ferroportin (Fpn) and occluded its iron export activity, thereby revealing a previously unrecognized mechanism for Fpn regulation.[1]

Fpn, the sole iron exporter known in vertebrates to date, is highly expressed in intestinal epithelial cells, reticuloendothelial macrophages, and hepatocytes to regulate iron absorption, recycling, and storage. Hepcidin, a small peptide hormone secreted by hepatocytes, regulates the abundance of Fpn in response to iron overload, inflammation, and erythropoiesis to optimize systemic iron homeostasis.[2] In the circulation, hepcidin binds to Fpn on the plasma membrane to induce its ubiquitination, internalization, and degradation, which reduces iron influx to the blood. Gene mutations that either disrupt hepcidin expression or change Fpn activity cause hereditary iron disorders, emphasizing the essential role of the hepcidin-Fpn axis in systemic iron hemostasis. Fpn mutations are a common cause of hemochromatosis.[3] Gain-of-function mutations that impair Fpn degradation cause high intestinal iron uptake, iron overload in hepatocytes and other tissues, high transferrin saturations, and iron deficiency in macrophages.[3] Conversely, loss-of-function mutations that reduce Fpn activity result in iron overload in reticuloendothelial macrophages, hyperferritinemia, and low to normal transferrin saturations.

Aschemeyer et al analyzed gain-of-function Fpn mutations in stably transfected cell lines. They found that these mutations either impaired hepcidin binding to Fpn or interfered with Fpn ubiquitination and degradation following hepcidin treatment.

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