Efficacy in the margins of NHL with ibrutinib

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MZLs are a group of non-Hodgkin lymphomas (NHLs) divided into nodal, extranodal, and splenic entities in the World Health Organization classification system. They are among the most indolent of the NHLs, having a median overall survival ranging from many years to more than a decade. The recognition that some MZLs rely on a continuous antigenic exposure for disease pathogenesis has led to successful treatment aimed at eliminating the oncogenic stimulus. Examples include Helicobacter pylori–directed therapy in the case of gastric lymphoma of mucosa-associated lymphoid tissue (MALT) and antiviral therapy for hepatitis C–related cases. However, for the nodal and splenic MZLs or in cases of disseminated MALT lymphomas, cure is not typically achievable, and systemic therapy is ultimately required.

Few clinical trials have focused on MZL. Data supporting the use of systemic therapy have been based on studies enrolling several indolent NHL subtypes, of which MZL typically represents a small proportion. High response rates are observed for chemoimmunotherapy in the first-line setting. However, relapse occurs in the majority of patients. In an effort to identify novel targets and improve therapeutic options, transcriptomic analyses have been performed that identify frequent deregulation of NF-κB, JAK/STAT, NOTCH, and Toll-like receptor signaling pathways as contributors to marginal zone lymphomagenesis. Although such analyses have also identified aberrations downstream of the B-cell receptor (BCR), somatic mutations of key regulators such as CARD11, MYD88, and TNFAIP3 have been observed in only a minority of patients. Nonetheless, the role of antigenic stimulation via BCR in driving MZL proliferation suggests that investigations targeting this pathway are warranted.

With this in mind, phase 1 testing of ibrutinib demonstrated responses across lymphoma subtypes, including an objective response in 1 of 4 MZL patients enrolled. The accompanying article by Noy et al reports on the subsequent effort to better understand the utility of ibrutinib in this lymphoma histology. Of the 63 patients enrolled, half had extranodal MZL, and the remainder were split between splenic and nodal subtypes. The patients were not as heavily pretreated when compared with patients in other studies of relapsed lymphoma, with a median of 2 prior therapies, 63% having received chemoimmunotherapy, and only 22% being refractory to their most recent therapy. Perhaps this is not surprising, given the indolent nature of the disease, favorable responses to anti-CD20 therapy, and a lack of approved targeted agents. The results demonstrate objective responses in just under half the patients and a median progression-free survival of 14 months. No difference in response rates was demonstrated by MZL subtype, number of prior regimens, or previous chemoimmunotherapy. However, the small numbers of patients in the subsets limit meaningful comparisons. Tolerability was similar to that in other ibrutinib trials with low rates of severe adverse events. The single bleeding-related mortality reminds us that caution should be exercised when administering ibrutinib with anticoagulation.

Putting these results into context, the efficacy of ibrutinib seems similar to that of other single agents evaluated in patients with relapsed MZL, including other agents that target molecules downstream of BCR. In addition, the toxicity profile of ibrutinib remains favorable in this population. Thus, the US Food and Drug Administration (FDA) has granted accelerated approval for ibrutinib in MZL patients previously treated with at least 1 prior anti-CD20–based therapy. Given the modest response rate when compared with other indications for which ibrutinib is approved, additional correlative studies that would help identify a predictive biomarker would add significantly to this work. Such efforts have been used to predict for efficacy in Waldenström macroglobulinemia and to guide ongoing studies in diffuse large B-cell lymphoma.

Nonetheless, the study team should be congratulated. Their trial demonstrates the ability to investigate rare disease subtypes in multicenter collaborations. The results justify ibrutinib as the first FDA-approved therapy for this disease and form the basis for subsequent trials that combine ibrutinib with anti-CD20 monoclonal antibodies and other targeted agents.
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**Multiple myeloma cells sent “PAKing”!**

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In this issue of Blood, Fulciniti et al report on the role of p21-activated kinase 4 (PAK4), a member of the p21-activated kinases family, in myeloma cell survival and proliferation. They also describe the effects of a novel allosteric inhibitor of PAK4 that is currently in early phase 1 trials.1

The 6 hallmarks of cancer highlight the quintessential role kinases play in the signal transduction across complex and deregulated networks of circuits required for cancer cell survival, proliferation, motility, and invasion.2 Therefore, pharmacologic drugging of these kinases represents an attractive and logical target, but not without 2 major challenges. The first stems from the kinases’ ubiquitous tissue distribution among transformed and normal cells, and the second from achieving kinase selectivity due to the evolutionary conservation of the adenosine triphosphate (ATP)–binding pocket among kinases.

The PAKs were first discovered in 1994 with the identification of PAK1 in a screen for proteins that interact with the small G-proteins, Rac1 and Cdc42.3 Currently, the PAKs family consists of 6 mammalian serine/threonine kinases grouped into 2 subfamilies, based on their domains’ structural homology and regulatory mechanisms. Group I PAKs (PAK1-3) are activated upon binding the β-family of GTPases, Cdc42 and Rac1, whereas group II PAKs (PAK4-6) are constitutively phosphorylated and active, independent of GTPases.4 PAKs group I and II have been implicated in the pathogenesis of several malignancies.5 In the particular case of the PAKs family member PAK4, it was initially recognized as a key mediator of Ras signaling, Ras-mediated cellular transformation, and in vivo tumorigenesis. In addition, PAK4 represents an essential node in cancer cells’ circuits regulating proliferation (G1 phase cell cycle progression and mitotic spindle formation), apoptotic cell death effectors (BCL2-associated agonist of cell death [BAD] phosphorylation and caspase 8 cleavage), and the transduction of survival signals activating the nuclear factor (NF)–κB, MEK-extracellular signal-regulated kinase (ERK), and WNT/β-catenin pathways.6,7 Lastly, it is important to note that PAK4 genomic locus (19q13.2) is frequently amplified in several tumors, including multiple myeloma (MM).

In light of the strong evidence implicating PAK4 in cancer pathogenesis, it is not surprising that a number of PAK family inhibitors have been developed, of which only one, the ATP-competitive PAK4 inhibitor (PF-3758309; Pfizer), was clinically tested in a phase 1 trial. However, the development of this compound was prematurely halted due to undesirable pharmacokinetics (low human bioavailability) and lack of a dose-response effect despite very promising preclinical activity.8 It is important to note here that the phenotype of PAK4-null mice, which is embryonically lethal, involves fetal heart defects as well as abnormal neuronal development. Therefore, the clinical safety and feasibility of such an approach targeting PAK4 is yet to be clinically demonstrated, and hence the relevance of the work reported in this issue of Blood by Fulciniti et al describing the effects of a novel allosteric PAK4 inhibitor KPT-9274 in MM.

Similar to the role of PAK4 in other malignancies, PAK4 is here reported to be expressed in most myeloma cell lines and primary myeloma cells, and it is demonstrated to regulate myeloma cells proliferation and survival through activation of the NF-κB and MEK-ERK canonical pathways. The authors also describe, in a series of quantitative proteomics and coimmunoprecipitation experiments, the selective affinity of KPT-7523 (Karyopharm) for the PAKs group II family member PAK4. Consistent with its
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