This large retrospective series included patients treated from 2002 to 2015 and excluded patients with acute myeloid leukemia (AML)– or ALL-specific transcripts and BCR-ABL$^+$ patients. The global outcome of ALAL was worse than that of common B-cell ALL, but better than AML. However, striking differences emerge when analyzing event-free survival and survival according to the type of therapy. Five-year event-free survival reached 80% in patients treated with ALL protocols, but was <40% in patients who received AML-type therapies. The outcome of patients treated with combined lymphoid and myeloid-directed therapies was in between. When focusing on patients with CD19$^+$ ALAL, the difference was even more striking in favor of ALL-type therapy. Further conclusions can be drawn from this tremendous collaborative work: when available, minimal residual disease provides prognostic information in this subset of patients, and postinduction therapy should be adapted according to known prognostic factors, including prednisone response and rearrangement of the MLL/KTM2A gene (see figure). The impact of more recently identified genomic factors such as IKZF1 has not been studied in this retrospective series. Allogeneic stem cell transplantation was clearly not mandatory in ALAL, but did help more chemoresistant patients. Treatment options for resistant patients must be approached with caution. For example, in bilineal ALAL, new salvage therapies such as blinatumomab or CD19-CAR-T might be inefficient on the CD19$^-$ cell component, thus supporting multivalent peptibody use.[6]

Finally, based on the results of the study, the authors propose a treatment algorithm that they recommend be tested in a prospective trial. This proposal sounds attractive and, given the paucity of ALAL patients, a common international trial based on the template in this paper would be most desirable.

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LYMPHOID NEOPLASIA

Comment on Phillips et al, page 293

PI3K inhibitors and the search for the Holy Grail

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In this issue of *Blood*, Phillips et al demonstrate an exciting approach to improve efficacy and decrease the toxicity of phosphatidylinositol 3-kinase (PI3K) inhibitors.[1] In the past decade, we have learned of the pivotal role PI3K plays in the growth and survival of many cancers, including B-cell malignancies. PI3Ks are also important in the microenvironment, where they have effects on recruitment and differentiation of cells that support the survival of the malignant B cells. There are 4 isoforms: α, β, δ, and ϒ. The expression of these isoforms varies by tissue. Preclinical models suggested that specifically inhibiting the δ isoform might provide significant efficacy in B-cell malignancies while decreasing potential toxicities of pan inhibitors because its expression is restricted to leukocytes. However, autoimmune problems, particularly colitis, were also seen in these preclinical models.[2] There are now 2 PI3K inhibitors that have received regulatory approval for the treatment of B-cell malignancies in the United States. The first was idelalisib, a PI3K δ isoform-specific inhibitor. The clinical results of idelalisib are very much in line with what one would have predicted from the preclinical studies, substantial efficacy in lymphoma and chronic lymphocytic leukemia, but also with the colitis, as seen in the mouse models. Liver toxicity has also been observed, which appears to be immune mediated.[3]

Unfortunately concern about the adverse event profile has tempered enthusiasm for idelalisib. Furthermore patients ultimately progress on idelalisib and thus more work needs to be done to improve both its tolerability and efficacy. Copanlisib was recently approved for the treatment of relapsed indolent lymphoma. Although it inhibits all 4 isoforms of the PI3K, its predominant effect is on the α and δ isoforms. This drug has a unique safety profile. Although the gastrointestinal adverse events such as transaminitis and colitis are substantially lower, other adverse events including hyperglycemia have been observed.[4] The hyperglycemia is likely secondary to inhibition of PI3K α, which is known to be involved in glucose metabolism. The decreased incidence of colitis may be due to the broader inhibitor of PI3K of copanlisib; alternatively, it may be from the intermittent dose schedule that has been used compared with the continuous inhibition produced by idelalisib with the currently used doses and schedule.

The tradeoff with therapies that are very specific for 1 target is the potential for resistance through alternative pathways. In this issue, Phillips et al present an interesting phase 1 study in which a JAK1 inhibitor, itacitinib, is combined with a novel PI3K δ inhibitor, INCB040093. Inhibition of the JAK-STAT pathway is a potential alternative approach to the treatment of B-cell malignancies and complementary

to PI3K inhibition. Although the design of this phase 1 study did not permit any firm conclusions regarding efficacy, these investigators did demonstrate an increase in response with the combination of the JAK1 inhibitor and the PI3K δ inhibitor in patients with classical Hodgkin lymphoma. In this histology, the overall response rate of 67% was seen with combination compared with 27% with single-agent INCB040093. Further study will be needed to confirm this observation; unfortunately, the activity was not as robust in histologies other than Hodgkin lymphoma.

One principle in developing combination therapies for cancer is to combine drugs that have minimal overlapping toxicities. However, even when the single-agent profiles suggest that 2 medications can be combined, there are sometimes unforeseen toxicities. An example of this is the combination of a syc inhibitor with idelalisib. This combination produced a significant increase in pneumonitis, rendering the combination unviable.[5] However, in the study by Phillips et al, the opposite was seen. The combination of itacitinib with INCB040093 appears to decrease the hepatotoxicity seen with single-agent INCB040093. The authors hypothesize that the anti-inflammatory effect of the JAK1 inhibitor prevented the increase in aminotransferases commonly seen with PI3K δ inhibitors. This approach is intriguing. Using a second agent to not only increase the efficacy of PI3K inhibitors, but also decrease the toxicity is important and might ultimately broaden their role in the treatment of patients with B-cell malignancies. Interestingly, similar findings were recently reported with a combination of duvelisib, a dual inhibitor of PI3K δ and ϒ, and romidepsin in patients with T-cell malignancies.[6] The combination improved the response rate decreased liver toxicities. There are of course other potential explanations for the findings of Phillips et al. The rate of liver function abnormalities with PI3K δ inhibitors appears to vary with the number and type of prior therapies as well as the histology. The number of patients treated in this phase 1 study was relatively small, and this finding will require further study. It is also not clear whether the addition of the JAK 1 inhibitor will prevent some of the late complications of PI3K δ inhibition, such as colitis. However, it is clear that this combination is immunosuppressive. Five patients developed *Pneumocystis* pneumonia before mandatory prophylaxis was instituted. Although *Pneumocystis* pneumonia is largely preventable with prophylaxis, it does raise the concern that other opportunistic infections might occur.

The PI3K play an important role in both low grade and aggressive B-cell malignancies. However, their use has been limited by some of their associated adverse events. Finding ways to improve their tolerability and efficacy are important. Combining PI3K inhibitors with other therapies may be one such approach to increase efficacy and decrease toxicity, the Holy Grail of drug development.

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MYELOID NEOPLASIA

Comment on Bhatia et al, page 307

HSP90 inhibition without heat shock response

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In this issue of *Blood*, Bhatia and colleagues describe a heat shock protein 90 (HSP90) C-terminal dimerization inhibitor with mechanistic differences that distinguish it from other clinically unsuccessful N-terminal ATPase binding compounds.[1] Can graveyard raiding of an old therapeutic target with a new strategy bring long awaited success?

Developing targeted therapeutics for cancer is quite complicated because multiple redundant mechanisms bypass that particular agent's target of action. In addition, many therapeutic targets relevant to cancer also have normal functions that prevent targeting with small molecules. No such target more represents this dilemma than HSP90. HSP90 represented a promising target because multiple mutated or aberrantly expressed oncogenes depend on HSP90 for protein stabilization. Based on structural variations induced by their activating mutation, there was a rush to develop agents that inhibited HSP90, which should cause destabilization of oncogene-induced proteins. Such drugs would be hypothesized to have a dramatic clinical benefit, even in the presence of mutated oncogene proteins not responsive to standard kinase inhibitors. In addition, as many mutated proteins depend more on HSP90 for stabilization and tumors have been reported to have