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

more active HSP90 ATPase activity,[2] multiple animal studies demonstrated that a significant therapeutic window existed between the mutated proteins and the normal homolog proteins, thereby yielding an acceptable therapeutic index.[3] Unfortunately, clinical trials of multiple different HSP90 inhibitors were unsuccessful due to both lack of clinical efficacy and toxicity. Some of these toxicities, including night blindness[4,5] and cardiac toxicity,[6,7] are unacceptable findings, which ultimately have prevented therapeutics from moving forward. How can such a promising target so utterly fail?

Bhatia and colleagues provide insight on why previous HSP90 inhibitors have failed, and based on this insight, developed a peptide inhibitor that prevents dimerization of the C-terminal portion of HSP90. Virtually all HSP90 inhibitors developed to date bind in the ATP binding site in the N-terminal domain of HSP90 protein. Although inhibiting HSP90, this yielded an HS1 transcriptional response, which activated alterative heat shock proteins (HSP70, HSP40, or HSP27) with either redundant or compensatory antiapoptotic function, thereby maintaining the stability of mutated proteins and/or preventing cell death. Utilizing a different strategy, Bhatia and colleagues used structural combinatorial monitoring to develop small peptides, which prevent dimerization of HSP90 protein in the C-terminal region of the protein. This novel approach with their peptide compound aminoxyrone did not promote an HS1 transcriptional response and resistance to cancer cell death, as seen with earlier compounds explored by others. The authors show also that aminoxyrone is effective in preclinical models of chronic myeloid leukemia (CML) similar to N-terminal–directed HSP90 inhibitors.[8,9] Unlike these older agents, aminoxyrone does not promote an HS1 response. Aminoxyrone also effectively depleted BCR-ABL–containing CML stem cells, the cellular origin of this disease that requires long-term treatment with BCR-ABL–targeted therapeutics such as imatinib. For a well-characterized oncogene-driven disease, this aminoxyrone was effective in vitro. In addition, aminoxyrone was shown to have in vivo activity in a K562 cell line model with evidence of tumor pharmacodynamic modulation of STAT5a and Crkl phosphorylation without modulation of other HS1 targets. Supporting data are also provided from primary tumor cells derived from tumors with other mutated oncogenes, including FLT3 ITD$^+$ acute myeloid leukemia and Philadelphia chromosome–like acute lymphoblastic leukemia. In addition, preclinical activity was also shown with chronic lymphocytic leukemia, a disease consistently demonstrated to be sensitive in vitro to HSP90 inhibition.[10]

Where does aminoxyrone as a therapeutic go from here? Although in vivo activity was demonstrated against the K562 cell line in vivo, it is unlikely that the supramolar concentrations required will allow effective translation to clinical trials in patients. Peptide therapeutics are challenging to develop due to production issues, cellular penetration, and delivery. Even if aminoxyrone cannot be translated to the clinic, this study shows that derivative molecules that bind to the C-terminal region of HSP90 and prevent dimerization may have a favorable clinical impact on cancers dependent on HSP90 client proteins, which often represents an active oncogene. Provided preclinical toxicity, pharmacology, and pharmacodynamic studies of these compounds look favorable, it will lie upon the pharmaceutical developers to move forward with the initial phase 1 trials despite multiple negative HSP90 inhibitor trials published to date. The concept presented in this paper differentiating aminoxyrone as a HSP90 C-terminal dimerization inhibitor justifies this and gives hope that a long described therapeutic target for cancer might actually come to fruition.

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