IN THE SPOTLIGHT

Bcl-2 Inhibition or FBXW7 Mutation Sensitizes Solid Tumor Cells to HDAC Inhibition In Vitro but Could Prove Difficult to Validate in Patients

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Summary: In this issue of Cancer Discovery, He and colleagues determined that Mcl-1 levels are a key factor in the response to histone deacetylase (HDAC) inhibitors, and FBXW7 mutation is a biomarker for sensitivity to HDAC inhibition. They also present evidence for synergy between treatment with HDAC inhibitors and Bcl-2–targeted therapeutics. These data provide an exciting new biomarker and combination therapy that should be evaluated clinically. Cancer Discov; 3(3); 258-9. ©2013 AACR.

See related article by He et al., p. 324 (4).

Head and neck squamous cell carcinoma (HNSCC) is composed of a diverse group of tumors from the upper aerodigestive tract with poor survival, few useful biomarkers, and even fewer targeted therapeutics (1). Recent genomic analyses of HNSCC have identified many genomic alterations in this disease (2, 3), but the majority of these events do not lend themselves directly to targeted therapeutic intervention (i.e., TP53 mutation). This leaves the path toward novel targeted treatments still uncertain.

He and colleagues (4) begin by examining the sensitivity of HNSCC and esophageal SCC cell lines to vorinostat, a histone deacetylase (HDAC) inhibitor. Vorinostat is approved by the U.S. Food and Drug administration for use in cutaneous HNSCC and esophageal SCC cell lines to vorinostat, a histone deacetylase (HDAC) inhibitor. Vorinostat is approved by the U.S. Food and Drug administration for use in cutaneous HNSCC (6), but it has generally shown poor efficacy in the treatment of solid tumors (7). The authors indicate that sensitivity to vorinostat is associated with the levels of the apoptotic inhibitors Bcl-2 and Mcl-1 in these cell lines. Overexpression of Bcl-2 has previously been shown to cause resistance to vorinostat (7), but here, the sensitivity is revealed to be functionally dependent on Mcl-1 as well.

Bim is an activator of apoptosis that can be bound to and inhibited by both Bcl-2 and Mcl-1 (8). Bim is primarily bound to Mcl-1 in these cells. It was found that vorinostat treatment reduces the level of Mcl-1 and thus displaces Bim from Mcl-1 to Bcl-2. Eventually, much Bim is displaced from Mcl-1 that Bcl-2 becomes saturated and free Bim is able to induce apoptosis. In this way, vorinostat sensitivity is associated with both Mcl-1 and Bcl-2 levels. How vorinostat decreases Mcl-1 levels is still unknown, as this could occur either in a chromatin-dependent manner or through a more direct effect on Mcl-1 protein or one of its regulators. Because HDAC inhibitors can have many cellular effects, it is important to have identified 2 key proteins in the response of these cells.

On the basis of an analysis of an outlier cell line, it was determined the FBXW7 (cde4, FBW7) mutation increases the levels of Mcl-1 and Bim and increases sensitivity to vorinostat. FBXW7 is an E3 ubiquitin ligase that regulates the stability of many proteins, including cyclin E1, c-Myc, NOTCH1, and Mcl-1 (9). Mutations in FBXW7 usually disrupt 3 key residues in the substrate-binding domain and lead to increased stability of target proteins. Many of the FBXW7 targets are known oncogenes, so these mutations could promote tumorigenesis through multiple pathways. Recent exome sequencing of HNSCC identified FBXW7 mutations in 5% of tumors, but the key oncogenic target of these events was unknown (2). He and colleagues (4) identify Mcl-1 as the first functional and biologically relevant target for FBXW7 in HNSCC. Excitingly, they also link the mutation to increased sensitivity to a therapeutic intervention. Although vorinostat did not perform well in a small trial of HNSCC (6), it would be interesting to test vorinostat in a cohort selected for FBXW7 mutations. FBXW7 mutations have also been found in other solid tumor types (pancreatic, prostate, endometrial, and others), and it may be useful to examine vorinostat in genomically selected patients from those tumor types as well (9, 10). This adds FBXW7 mutation to a rapidly growing list of genomic alterations that are found at low frequency in many tumor types and may be therapeutically targetable. These genes present a challenge for clinical trial design because not enough patients for each tumor site may be identified to show efficacy. Much discussion has taken place about “tissue agnostic” clinical trials, in which patient selection is based on the genomic alteration instead of the tissue type (11, 12), and if a framework for these kinds of trials can be developed, FBXW7 may be another gene to examine in that format.

Although it is generally difficult to therapeutically target the loss of a tumor suppressor gene, this case shows that in some instances the resulting activation of an oncogene may be therapeutically useful. This approach is attractive in HNSCC, in which the majority of genomic alterations occur in tumor suppressor genes, and it is hoped that more pathways like this one can be identified and targeted.
He and colleagues from the Ellisen laboratory also noticed that the mechanism of apoptotic regulation in these cells lends itself to combination therapy (4). Because HNSCC cells are dependent on Bcl-2 to inhibit Bim, then the combination treatment with a Bcl-2 inhibitor should sensitize these cells to vorinostat. One class of Bcl-2 inhibitors is the BH3-mimetic drugs that displace Bim from BH3-containing proteins like Bcl-2 and Mcl-1 (13). These drugs are being developed for use in the treatment of cancer, and ABT-737 is a BH3 mimetic with a high affinity for Bcl-2, but not for Mcl-1. The authors show that ABT-737 and vorinostat synergize in vitro and lead to tumor shrinkage in a xenograft model (4). This mechanistically designed combination therapy is not obvious from the canonical functions of these drugs, and it shows the importance of mechanistic studies of the biology of inhibitors, even in tumors for which they have shown minimal clinical efficacy.

This work is a stark reminder of the forthcoming challenges in using targeted therapeutics for patients with cancer. Both drugs used in this article are likely to fail (or have already failed) in single-agent trials in HNSCC. Only the combination therapy is expected to show benefit. However, it is very difficult to initiate a clinical trial using 2 failed therapeutics. The current approval systems are not set up for genomically driven mechanistically designed therapeutic combinations with minimal single-agent efficacy. It is anticipated that findings like these will soon become common, and it will be a great loss if a clinical trials system is not developed to take advantage of them.

Finally, the system described here begins to clarify the difference in sensitivity of solid tumors and hematopoietic tumors to Bcl-2 inhibition and possibly HDAC inhibitors. In HNSCC, it seems that the Mcl-1/Bcl-2 ratio may be the key factor in sensitivity, rather than purely Bcl-2 levels. The levels of Bcl-2 are much lower in HNSCC compared with those in leukemia, and this makes the HNSCC cells also dependent on Mcl-1. Because Mcl-1 acts as a sink for Bim, single-agent Bcl-2 inhibitors may be insufficient to activate apoptosis in solid tumors. Conversely, the higher levels of Bcl-2 in leukemia cells make them susceptible to single-agent Bcl-2 inhibition. A large difference (10-fold) was observed in the IC$_{50}$ values for HNSCC cells and hematopoietic cells. Understanding this signaling relationship opens up new possibilities for synergy in combination drug treatments. Other drugs that disrupt the levels of Mcl-1, Bcl-2, or Bim may synergize with either vorinostat or ABT-737. Similarly, genomic alterations that disrupt this pathway may also lend themselves to specific interventions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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