Tales of How Great Drugs Were Brought Down by a Flawed Rationale—Letter

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In their recently published article (1), Komlodi-Pasztor and colleagues propose that development of selective mitotic inhibitors is grounded in a flawed therapeutic rationale. The authors argue that the primary determinant of sensitivity is tumor cell proliferation rate, and that these drugs may prove efficacious only in highly proliferative disease. However, it is clear that variations in apoptotic signaling pathways can also play an important role in tumor sensitivity.

As Komlodi-Pasztor and colleagues note, drug-induced mitotic arrest is usually transient, with cells subsequently undergoing apoptosis or exiting into interphase without cell division (mitotic slippage). Using one class of mitosis-specific drugs, inhibitors of the mitotic kinesin KSP, we and others have shown that the commitment to initiate apoptosis following mitotic arrest is accompanied by loss of critical survival signals (2, 3). For example, cells that selectively depend on the antiapoptotic protein Mcl-1 for survival and can degrade Mcl-1 during mitosis undergo apoptosis in response to KSP inhibition. Among normal tissues, Mcl-1 is principally expressed in hematological progenitors. Myelosuppression is a predominant side effect of microtubule targeted agents and targeted antimitotic therapies, including KSP inhibitors, consistent with reliance of neutrophil progenitors on Mcl-1 for survival. Tumors exhibiting a similar reliance upon Mcl-1 might be expected to reveal comparable sensitivity to KSP inhibition, irrespective of proliferation rate. Such diseases include hematological cancers, as well as select solid tumors (4).

Recent clinical development of targeted antimitotics has included disease settings with selective reliance on Mcl-1 for survival during mitosis, many of which are not highly proliferative. For example, a phase II study of the KSP inhibitor ARRY-520 in heavily pretreated patients with multiple myeloma reported an overall response rate of 18%, similar to the reported activity of proteasome inhibitors and IMiDs (5). Myelomas are typically slowly proliferating, inconsistent with the hypothesis that targeted antimitotics should exhibit activity only in highly proliferative diseases. In this setting, sensitivity to KSP inhibition may be a consequence of reliance on Mcl-1 for survival during mitosis.

Proliferation rate is likely to be an important determinant of tumor sensitivity to antimitotic therapies. Clinical findings with ARRY-520 suggest that additional pathways, including apoptotic signaling, also play key roles in disease response to these novel therapies and support a broader therapeutic opportunity for antimitotics than just highly proliferative indications.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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