Targeted Therapy

Major finding: Reverse engineering of navitoclax identified a BCL-2–selective inhibitor that does not kill platelets.

Concept: Navitoclax blocks the activity of both BCL-2 and BCL-XL, the primary platelet survival factor.

Impact: A selective BCL-2 inhibitor can be used at relatively high doses without causing thrombocytopenia.

BCL-2–SELECTIVE INHIBITORS SPARE PLATELETS

Prosurvival BCL-2 family proteins that mediate evasion of apoptosis are often required for cancer cell survival and represent attractive therapeutic targets. The orally bioavailable small molecule navitoclax (ABT-263) inhibits the antiapoptotic activity of the highly related proteins BCL-2 and BCL-XL and has shown clinical activity in BCL-2–dependent hematologic cancers. However, BCL-XL is also a key survival factor for platelets, and BCL-XL inhibition by navitoclax leads to a rapid decrease in circulating platelets, or thrombocytopenia, that limits dosing. Souers and colleagues therefore hypothesized that a selective BCL-2 inhibitor might be used at more effective doses in BCL-2–dependent cancers without on-target thrombocytopenia. Systematic removal or replacement of navitoclax moieties to identify features that increased BCL-2 selectivity led to the discovery of ABT-199, a small molecule with subnanomolar affinity for BCL-2. ABT-199 potently disrupted BCL-2 function and induced apoptotic cell death, particularly in leukemia and lymphoma cells with high BCL-2 expression. Single-agent ABT-199 suppressed growth of several hematologic tumor xenograft models in a dose-dependent manner and potentiated the activity of clinically relevant chemotherapies and immunotherapies such as bendamustine and rituximab. Importantly, ABT-199 was significantly less active against human platelets *ex vivo* than navitoclax and could be used at much higher doses in dogs without appreciable effects on circulating platelets, suggesting that efficacious plasma concentrations of ABT-199 might be attained without platelet damage. Indeed, in a first-in-human trial in 3 patients with refractory chronic lymphocytic leukemia, a single dose of ABT-199 induced tumor lysis in all 3 patients within 24 hours with minimal effects on platelet counts. BCL-2–selective inhibition may therefore be feasible for treatment of BCL-2–dependent cancers and avoid on-target toxicity associated with inhibition of BCL-XL. ■

Souers AJ, Leverson JD, Boghaert ER, Ackler SL, Catron ND, Chen J, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013;19:202–8.

Drug Resistance

Major finding: Intermittent vemurafenib dosing prevents resistance in primary human melanoma xenografts.

Concept: Vemurafenib-resistant melanoma cells require vemurafenib for proliferation and survival.

Impact: Discontinuous dosing regimens may defer resistance and prolong responses to targeted therapies.

DISCONTINUOUS VEMURAFENIB DOSING DELAYS RESISTANCE

Targeted inhibition of BRAF with vemurafenib leads to tumor regression and prolonged survival in many patients with *BRAF*-mutant metastatic melanoma, but lethal drug-resistant disease almost invariably emerges. Das Thakur and colleagues recapitulated acquired vemurafenib resistance by continuously treating mice bearing a vemurafenib-naïve, patient-derived *BRAF*-mutant melanoma with vemurafenib until drug resistance developed. Surprisingly, cell lines derived from the drug-resistant tumor could not be established in the absence of vemurafenib. Furthermore, withdrawal of vemurafenib from established cell lines resulted in changes in cell morphology and decreased proliferation caused by elevated ERK signaling, suggesting that the vemurafenib-resistant melanoma cells had become dependent on vemurafenib-mediated modulation of ERK signaling levels. Consistent with these findings, cessation of vemurafenib treatment in mice carrying vemurafenib-resistant melanomas led to tumor regression within 10 days, although tumors eventually resumed growing. These results suggested that intermittent dosing of vemurafenib might create an unfavorable environment for drug-resistant cells and delay the onset of lethal drug resistance. To test this hypothesis, mice bearing primary human melanoma xenografts were given vemurafenib daily on either a continuous or intermittent (4 weeks on, 2 weeks off) schedule. Mice receiving continuous vemurafenib developed lethal drug-resistant disease with 100 days, whereas none of the mice on the intermittent dosing schedule developed resistant disease after 200 days of treatment. These findings indicate that continuous vemurafenib treatment selects for drug-resistant cells but that a discontinuous dosing schedule may select against drug-resistant cells and prolong the responses to vemurafenib therapy. Further studies are warranted to determine whether such altered vemurafenib dosing will be beneficial in patients with *BRAF*-mutant melanoma and if these observations are applicable to other targeted therapies. ■

Das Thakur M, Salangsang F, Landman AS, Sellers WR, Pryer NK, Levesque MP, et al. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. Nature 2013;494:251–5.