Will Hsp90 Inhibitors Prove Effective in BRAF-Mutant Melanomas?

Federica Catalanotti\textsuperscript{1} and David B. Solit\textsuperscript{1,2}

The RAF inhibitor vemurafenib has unprecedented activity in BRAF-mutant melanomas, but resistance invariably develops. As Hsp90 is required for the stability of several of the oncoproteins that mediate RAF inhibitor resistance, inhibitors of this cellular chaperone may be effective in patients with intrinsic or acquired resistance to RAF inhibitors. \textit{Clin Cancer Res; 18}(9); 1–3. ©2012 AACR.

In this issue of \textit{Clinical Cancer Research}, Paraiso and colleagues (1) examine whether inhibition of Hsp90 can overcome RAF inhibitor resistance in BRAF-mutant melanomas. RAF inhibitors, including vemurafenib, recently approved by the U.S. Food and Drug Administration, have remarkable therapeutic effects in patients with BRAF-mutant melanoma (2). However, responses to vemurafenib are temporary and rarely complete, with a median time to progression of 6 to 7 months.

Recent laboratory and clinical studies have identified 2 general explanations for resistance to RAF inhibitors (Fig. 1). The first of these entails failure to inhibit RAF signaling to a sufficient degree to induce cell-growth arrest or cell death. Our group and others have shown that upstream activation of RAS [resulting from NRAS mutation or receptor tyrosine kinase activation (RTK)], overexpression of RAF1 or COT [a mitogen-activated protein (MAP)/extracellular signal-regulated kinase (ERK) kinase (MEK) kinase], or expression of RAF splice variants that dimerize in a RAS-independent manner are all resistance mechanisms that attenuate or prevent ERK inhibition by RAF inhibitors (3–6). As resistance in this setting results, at least in part, from a failure to effectively inhibit ERK signaling, such tumors may retain sensitivity to inhibitors of downstream effectors of RAF transformation, such as MEK, a hypothesis currently being tested in ongoing clinical trials. The second class of RAF inhibitor–resistant mechanisms includes alterations that diminish the RAF dependence of the tumor. In this scenario, resistance often occurs despite effective inhibition of ERK signaling by the drug. One example would be activating mutations within the phosphoinositide 3-kinase (PI3K)/AKT pathway (7). In this latter setting, the combination of a RAF inhibitor and a PI3K or AKT inhibitor may prove effective.

Studies of RAF inhibitor resistance thus provide a rationale for combination treatment approaches that may prolong the duration of treatment response or identify novel drug targets for patients with acquired drug resistance. As more than one mechanism of vemurafenib resistance may coexist in a heterogeneous population of tumor cells, selectively targeting an individual resistance mechanism may have only limited clinical impact. With this limitation in mind, Paraiso and colleagues explored whether cotargeting multiple mechanisms of RAF inhibitor resistance through inhibition of the Hsp90 chaperone is a viable alternative approach. Hsp90 is a cellular chaperone required for the refolding of denatured proteins, cellular survival under stress conditions, and the maturation of a subset of proteins that play key roles in transducing proliferative and antiapoptotic signals. Several natural products (geldanamycin, radicicol) and small molecules (PU-71H, XL888, NVP-AUY922, STA-9090) bind to an ATP/ADP-binding pocket in the N-terminal domain of Hsp90 and inhibit its chaperone function (8). These compounds induce the degradation of Hsp90 “client” proteins, which include steroid receptors and a subset of tyrosine and serine/threonine kinases, including mutant, but not wild-type, BRAF (9).

To determine whether Hsp90 inhibition could overcome RAF inhibitor resistance, the authors studied a panel of melanoma cell lines that express the glutamate-to-valine substitution at codon 600 (V600E) BRAF mutation. This panel included BRAF V600E cells that were vemurafenib sensitive and cells that had been selected for resistance to the RAF inhibitor and coexpressed a NRAS mutation or had platelet-derived growth factor receptor B (PDGFR-B) activation. BRAF V600E melanoma cell lines with COT overexpression or CCND1 amplification that were intrinsically resistant to vemurafenib were also studied. In cell-culture studies, the proliferation and survival of all BRAF V600E cells examined were sensitive to the Hsp90 inhibitor XL888, with similar sensitivity noted in the cohorts that were vemurafenib sensitive and vemurafenib resistant. In vemurafenib-resistant cell lines, XL888 treatment resulted in...
reduced expression of several well-characterized Hsp90 clients, including insulin-like growth factor I receptor (IGF-IR) and AKT, as well as inhibition of both the ERK and AKT pathways. XL888 was also active against vemurafenib-resistant cell lines when grown as collagen-implanted 3D spheroids and induced the regression of subcutaneously grown xenografts. In summary, the data suggest that BRAF V600E melanoma cells that are resistant to vemurafenib as a result of a diversity of molecular changes retain sensitivity to Hsp90 inhibition.

Given these promising preclinical results, will Hsp90 inhibitors have meaningful clinical activity in patients with BRAF-mutant melanoma who exhibit clinical resistance to vemurafenib? Ultimately, the utility of Hsp90 inhibitors as clinical agents will depend on whether the degradation of Hsp90 clients key to tumor growth or survival occurs at drug concentrations that are tolerable to the patient. In the case of the geldanamycin derivative 17-AAG, provocative clinical activity has been shown in ERBB2-amplified breast cancers and in a small number of patients with non–small cell lung cancer with ALK fusions (10). These promising clinical results suggest that concentrations of 17-AAG sufficient to effectively downregulate the expression of HER2 and the ALK fusions that drive tumor progression in such patients can be achieved in at least a subset of patients. In patients with melanoma, however, 17-AAG was ineffective, and the drug’s lack of clinical activity was associated with its inability to durably downregulate the expression of BRAF V600E and RAF1 or durably suppress ERK activation in patients whose tumors were both BRAF-mutant and wild type (11).

Given the disappointing results with 17-AAG in vemurafenib-naive patients with BRAF V600E melanoma, is it reasonable to expect greater activity with Hsp90 inhibitors in patients with acquired resistance to vemurafenib? As Paraiso and colleagues noted similar sensitivity to Hsp90 inhibition in vemurafenib-resistant and
Will Hsp90 Inhibitors Prove Effective in BRAF-Mutant Melanomas?

In future trials incorporating Hsp90 inhibitors, the authors propose the use of a novel liquid chromatography, multiple reaction–monitoring mass spectrometry assay to quantify target inhibition in drug-treated patients. Unfortunately, the preclinical and clinical experience to date suggests that Hsp90 clients show variable sensitivity to Hsp90 inhibitor–induced degradation and that induction of Hsp70 and other HSP90-associated chaperones often occurs at drug levels significantly lower than those required for maximal antitumor effects (12). To ensure that the optimal dose and schedule are chosen for phase II testing, trials of novel Hsp90 inhibitors in patients with vemurafenib-resistant melanoma should, therefore, include the collection of pre- and posttreatment tumor biopsies to assess whether drug exposure is sufficient to induce the degradation of relevant Hsp90 clients and maximal inhibition of ERK signaling.

Disclosure of Potential Conflicts of Interest

D.B. Solit is a consultant for Roche. No potential conflicts of interest were disclosed by the other author.

Authors’ Contributions

Writing, review, and/or revision of the manuscript: F. Catalanotti, D.B. Solit

Received March 13, 2012; accepted March 14, 2012; published OnlineFirst March 22, 2012.

References

Will Hsp90 Inhibitors Prove Effective in BRAF-Mutant Melanomas?

Federica Catalanotti and David B. Solit

*Clin Cancer Res* Published OnlineFirst March 22, 2012.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-0626

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2012/04/25/1078-0432.CCR-12-0626.DC1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.