Response to Combined Molecular Targeting: Defining the Role of P-STAT3

Ann Marie Egloff and Jennifer R. Grandis

Abstract

Src family kinase (SFK)–targeting agents are currently undergoing clinical investigation for treatment of solid malignancies. Epidermal growth factor receptor (EGFR)–independent phosphorylation of STAT3 (P-STAT3) has been identified as a mechanism of tumor resistance to agents targeting SFK. Tumor P-STAT3 levels may be an important indicator of EGFR- and SKF-targeted antitumor treatment efficacy. Clin Cancer Res; 17(3); 393–5. ©2011 AACR.
combination of 2 agents. Both cell lines also exhibited significant reduction in xenograft tumor growth with the triple agent combination compared with single or dual agent treatment and a corresponding reduction in P-STAT3 tumor levels. However, in vitro cell viability assays following single or combined agent treatments showed no statistically significant reduction in cell viability with the triple combination compared with dual agent treatment. These data are an example of the incompletely understood discordance between in vitro cell viability and in vivo xenograft tumor growth, suggesting the limitations of preclinical models.

Although the combination of erlotinib, dasatinib, and gemcitabine resulted in reduced xenograft tumor volumes for both the sensitive and insensitive cell lines, the mechanism of action of was largely undefined. Image analysis of the xenograft tumors indicated that pAKT, pSFK, Ki67, and caspase 3 levels in both xenograft tumor types were not altered from dasatinib-erlotinib treatment levels by the addition of gemcitabine, yet P-STAT3 levels in both tumor types were markedly reduced following the triple agent treatment compared with single or any dual agent treatment. Given the pleiotropic actions of gemcitabine, it is difficult to speculate about the precise mechanism of P-STAT3 abrogation. However, STAT3 is activated and, hence, tyrosine phosphorylated downstream of both EGFR and SFKs. Thus, dual inhibition of EGFR and SFK provides more potent blockade of STAT3 activation. In HNSCC, the activation of STAT3 following knockdown of c-Src with small interfering RNA (siRNA) has been reported to be JAK dependent and result from reduced suppressor of cytokine signaling 2 (SOCS2) expression (6). Whether the activation of STAT3 following dasatinib treatment in pancreatic cancer cells results from the same alterations in JAK and SOCS2 activities is unknown. Like many malignancies, pancreatic cancers have been reported to be genetically heterogeneous (7). The mechanisms contributing to STAT3 activation and the ability of combined treatment with erlotinib, dasatinib, and gemcitabine to reduce P-STAT3 may contribute to the success of this therapeutic strategy across heterogeneous pancreatic cancers. It is possible that the addition of gemcitabine to EGFR and SFK cotargeting may have utility for treatment of other cancers in which treatments combining EGFR- and SFK-targeting agents are being clinically evaluated, including NSCLC, HNSCC, and colorectal cancers. More generally, STAT3 phosphorylation has been identified as a mechanism of resistance to SFK-targeted therapies, but the precise contribution of STAT3 phosphorylation and/or activation to cancer therapy resistance remains unknown.

As has often been the case with targeted therapies, heterogeity of sensitivities to the 3 agents was observed among the panel of cell lines evaluated by Nagaraj and colleagues, but no identified correlation with baseline levels of c-Src, EGFR, or their phosphorylated forms was observed. In clinical trials to date combining erlotinib with gemcitabine for the treatment of pancreatic cancer, neither tumor EGFR gene amplification nor KRAS mutation status was found to be associated with treatment response to combined erlotinib-gemcitabine treatment (8, 9), and pancreatic cancers have been reported to very rarely harbor erlotinib-sensitizing EGFR-activating mutations (8). Although tumor biomarkers associated with response and/or resistance to EGFR-targeted therapies have been identified for NSCLC and colorectal cancers (10), no biomarker has yet been identified to be associated with response to SFK-targeting agents in patients with any solid tumor (11).

Clinical trials evaluating combined EGFR- and SFK-targeting agents are currently in phase I-II. One phase I-II clinical study evaluating dasatinib with erlotinib for treatment of 34 NSCLC patients reported 2 partial responses in which this regimen was tolerated (12). Two phase I-II trials combining SFK- and EGFR-targeting agents are currently...
ongoing (1): combining dasatinib with erlotinib for NSCLC and (2) combining dasatinib with cetuximab and radiation with or without cisplatin for patients with locally advanced HNSCC. However, there is a need to prospectively define responsive patient subpopulations. P-STAT3 levels in early post-treatment tumor biopsies have potential as a predictive biomarker, but these correlative studies may be difficult even for accessible tumors given the short biological half-life of dasatinib. More importantly, the response rates with combined EGFR- and SFK-targeted treatment in the NSCLC phase I-II study were modest. Identifying agents that abrogate P-STAT3 following combined EGFR- and SFK-targeted agents, such as gemcitabine in pancreatic preclinical models, may improve upon these response rates.

Disclosure of Potential Conflicts of Interest

A.M. Egloff and J.R. Grandis: commercial research grant, Bristol Myers-Squibb.

Received November 23, 2010; accepted December 7, 2010; published OnlineFirst January 25, 2011.

References

Clinical Cancer Research

Response to Combined Molecular Targeting: Defining the Role of P-STAT3

Ann Marie Egloff and Jennifer R. Grandis


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-10-2925

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2011/01/21/17.3.393.DC2

Cited articles
This article cites 9 articles, 6 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/17/3/393.full.html#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
/content/17/3/393.full.html#related-urls

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.