Usp44–/– bition did not correct the chromosome segregation errors in consistent with a modest checkpoint defect; however, APC inhibition did not correct the chromosome segregation errors in Usp44–/– MEFs, suggesting that USP44 modulates chromosome segregation errors during mitosis and suggest that loss of USP44 promotes genomic instability that enhances tumor growth.

Intriguingly, Usp44 preventive activity in CML cells and xenografts harboring drug-resistant kinase domain mutations, including the T315I mutant. Cortes and colleagues report findings from a multi-center phase I dose-escalation trial of ponatinib in which heavily pretreated patients with refractory CML were enrolled. The primary objective was to determine a maximum tolerated dose, and secondary endpoints included safety, antitumor activity, pharmacokinetics, and pharmacodynamics. Myelosuppression and low-grade skin disorders were the most common adverse events, and dose-limiting toxicities included elevated lipase or amylase and pancreatitis. Ponatinib reached serum levels sufficient for BCR–ABL inhibition in vitro and strongly reduced BCR–ABL target protein phosphorylation in a dose-dependent manner, indicating that the drug had on-target activity. Strikingly, of 43 enrolled patients with chronic-phase CML, 98% had a complete hematologic response, 63% had a complete cytogenetic response, 44% had a major molecular response, and the median duration of response had not yet been reached after more than 2 years of treatment. Among 12 patients with a T315I mutation, 100% had a complete hematologic response, and similarly high response rates were observed among patients with other BCR–ABL mutations or with no detectable mutations. Notably, major hematologic and cytogenetic responses were also observed in approximately one third of patients with advanced CML, which responds poorly to other tyrosine kinase inhibitors. Although further clinical testing is required, ponatinib shows promise for patients with resistant CML who lack other treatment options.


Clinical Trials

**Major finding:** Ponatinib elicits durable complete responses in heavily pretreated refractory CML.

**Concept:** Ponatinib is a potent inhibitor of all forms of BCR–ABL, including the T315I gatekeeper mutant.

**Impact:** Ponatinib is a third-generation tyrosine kinase inhibitor that may benefit patients with resistant CML.

**PONATINIB IS HIGHLY ACTIVE IN RESISTANT CHRONIC MYELOID LEUKEMIA**

Tyrosine kinase inhibitors that target the BCR–ABL fusion protein are highly effective in chronic myeloid leukemia (CML), but resistance can arise through mutation of the BCR–ABL kinase domain or other mechanisms. A particularly troubling mutation substitutes the threonine-315 gatekeeper residue with a bulky isoleucine that prevents drug binding and confers resistance to imatinib, dasatinib, and nilotinib. Ponatinib was identified as a small-molecule pan-BCR–ABL kinase inhibitor with preclinical activity in CML cells and xenografts harboring drug-resistant kinase domain mutations, including the T315I mutant. Cortes and colleagues report findings from a multi-center phase I dose-escalation trial of ponatinib in which heavily pretreated patients with refractory CML were enrolled. The primary objective was to determine a maximum tolerated dose, and secondary endpoints included safety, antitumor activity, pharmacokinetics, and pharmacodynamics. Myelosuppression and low-grade skin disorders were the most common adverse events, and dose-limiting toxicities included elevated lipase or amylase and pancreatitis. Ponatinib reached serum levels sufficient for BCR–ABL inhibition in vitro and strongly reduced BCR–ABL target protein phosphorylation in a dose-dependent manner, indicating that the drug had on-target activity. Strikingly, of 43 enrolled patients with chronic-phase CML, 98% had a complete hematologic response, 63% had a complete cytogenetic response, 44% had a major molecular response, and the median duration of response had not yet been reached after more than 2 years of treatment. Among 12 patients with a T315I mutation, 100% had a complete hematologic response, and similarly high response rates were observed among patients with other BCR–ABL mutations or with no detectable mutations. Notably, major hematologic and cytogenetic responses were also observed in approximately one third of patients with advanced CML, which responds poorly to other tyrosine kinase inhibitors. Although further clinical testing is required, ponatinib shows promise for patients with resistant CML who lack other treatment options.


**A DEUBIQUITINASE PROTECTS AGAINST ANEUPLOIDY AND TUMOR FORMATION**

Chromosome segregation errors during mitosis result in aneuploidy, which is present in many cancers and may contribute to tumorigenesis. The mitotic checkpoint prevents such errors by inhibiting the anaphase-promoting complex (APC), an E3 ubiquitin ligase that targets cyclin B1 and securin for degradation until all chromosomes are properly attached to the mitotic spindle. Zhang and colleagues investigated the role of the deubiquitinase (DUB) ubiquitin-specific protease 44 (USP44), which is thought to regulate this checkpoint by limiting APC activation, in mitosis. Although Usp44-deficient mice were viable, indicating that USP44 is dispensable for normal development, Usp44−/− mouse embryonic fibroblasts (MEF) exhibited an increase in chromosome missegregation and enhanced whole-chromosome aneuploidy, suggesting that USP44 is required to prevent mitotic errors. This phenotype was associated with more rapid progression through mitosis and faster release from mitotic arrest, consistent with a modest checkpoint defect; however, APC inhibition did not correct the chromosome segregation errors in Usp44−/− MEFs, suggesting that USP44 modulates chromosome stability independently of the mitotic checkpoint. USP44 deficiency resulted in abnormal spindle geometries early in mitosis, including incomplete separation and aberrant positioning of centrosomes, which were tightly correlated with formation of incorrectly attached lagging chromosomes. The regulation of chromosome segregation by USP44 required its localization to centrosomes via interaction with the centriole protein centrin 2 as well as its DUB activity. Intriguingly, Usp44−/− mice developed spontaneous tumors, in particular lung adenomas, at a much higher incidence compared with that of wild-type mice, and USP44 expression was decreased in human lung adenocarcinomas and associated with reduced overall survival, implicating USP44 as a tumor suppressor. These results identify a critical role for USP44 in mitosis and suggest that loss of USP44 promotes genomic instability that enhances tumor growth.

A Deubiquitinase Protects against Aneuploidy and Tumor Formation


Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-RW2012-217

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, use this link http://cancerdiscovery.aacrjournals.org/content/3/1/11.2. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.