Letters to the Editor

The Activity of Sunitinib against Gastrointestinal Stromal Tumor Seems to be Distinct from Its Antiangiogenic Effects

To the Editor: We read with great interest the work of Prenen et al. (1, 2), which revealed that the tyrosine kinase inhibitor sunitinib/SU11248 (Sutent; Pfizer, New York, NY), targeting KIT/CD117, vascular endothelial growth factor receptor (VEGF-R), platelet-derived growth factor receptor (PDGF-R), FLT3 (2), and possibly other cellular kinases (3), has clear in vitro efficacy against gastrointestinal stromal tumor (GIST) mutants refractory to imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp., Hanover, NJ). They showed that sunitinib had activity against KIT mutants but not against PDGF-R mutant GIST tumors. We have treated a number of patients with GIST tumors with sunitinib, and herein, we provide tumor biopsy results from one patient with an imatinib-refractory GIST tumor who had a marked tumor response to sunitinib treatment.1 We believe that this patient sheds further light on the mechanism of action of sunitinib in GIST, which appears to be by direct inhibition of tumor growth as opposed to an antiangiogenic mechanism.

The patient presented as a 59-year-old woman with a GIST tumor carrying the KIT genotype of an exon 11 deletion of 10 amino acids (550-559 KPMYEYQVKV); she underwent resection of a gastric primary tumor followed by recurrence in Morrison’s pouch 1 year later. She achieved a complete remission for 24 months while on treatment with imatinib. She continued on therapy for eight additional months with eventual progression of disease. A biopsy of the recurrence was done, and genotyping revealed that this tumor now carried the imatinib-resistant mutation T670I in exon 14. The patient was then initiated on sunitinib therapy receiving 50 mg orally per day on a schedule of 2 weeks on followed by 1 week off under an Institutional Review Board–approved protocol at Memorial Sloan-Kettering Cancer Center. A CAT scan was obtained just before treatment initiation and revealed an 8.1 × 5.6 cm mass in the left upper quadrant (Fig. 1A). This lesion was markedly diminished to 2.9 × 2.2 cm on a follow-up scan after 12 months of therapy (Fig. 1B). She subsequently underwent excision of the residual tumor.

To assess the effect of sunitinib on the imatinib-resistant tumor tissue and its blood supply, we undertook histologic and immunohistochemical analyses of formalin-fixed tissue specimens taken on biopsy immediately before treatment and just after completion of therapy. To assess either (a) tumor cells alone, (b) the combination of tumor cells and blood vessels, or (c) blood vessels alone, staining was done with anti-CD117 (polyclonal; DAKO, Carpinteria, CA), anti-CD34 (monoclonal QBEND10; Beckman-Coulter, Fullerton, CA), or anti-CD31 (monoclonal JC/70A; DAKO), respectively. Consistent with the patient’s clinical history and imaging results, we found a dramatic effect of sunitinib on the tumor parenchyma. Whereas the pretreatment biopsy revealed viable, mitotically active CD117+ and CD34+ tumor cells, the post-treatment specimen was >90% sclerotic and necrotic (Fig. 1C-F). Strikingly, the CD31+ blood vessels seemed robust both pretreatment and posttreatment and remained invested with likely pericytes and/or vascular smooth muscle cells (Fig. 1G-H). Vessel counts did not differ significantly before and after treatment by CD31 staining (P = not significant by Wilcoxon signed-rank test). Thus, the tumor cells were largely eliminated with sunitinib treatment, whereas feeding blood vessels were still present after 12 months of therapy. This observation supports the assertion that the mechanism of sunitinib in GIST is predominantly cytotoxic against the tumor by directly targeting KIT, and that an antiangiogenic effect, either through the VEGF-R2 in endothelium or through the PDGF-R in pericytes, seems to be secondary.

Sunitinib targets a subset of tyrosine kinases, including KIT, VEGF-R2, and the PDGF-R (2, 4), and it is important to determine the physiologically relevant targets in humans for each tumor type. This will allow for the identification of patients who are likely to respond to the drug. Sunitinib has been Food and Drug Administration approved for the treatment of imatinib-resistant GIST. In this imatinib-resistant GIST patient, we saw a dramatic clinical response to sunitinib without observing long-term destabilization of tumor blood vessels. Our observation in this patient is consistent with the results by Prenen et al. that KIT appears to be the predominant drug target in GIST (1). Furthermore, we suggest that the antiangiogenic mechanism of action of sunitinib is secondary.

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Fig. 1. Response to sunitinib with relative preservation of vasculature in GIST, pretreatment (A, C, E, and G) and posttreatment (B, D, F, and H). Pretreatment CAT scan revealed a large mass (A, red arrow) compared with posttreatment 12 months later (B). The response seems confined to the tumor parenchyma (necrotic) as opposed to the vascular compartment (intact, black arrows in D), seen by immunohistochemistry for CD117 (C and D), CD34 (E and F), or CD31 (G and H).
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