

Commentary

Tyrosine Kinase Inhibitor STI-571

The New Wonder Drug of Cancer Therapy

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Commentary to:

Inhibition of Cell Survival and Invasive Potential of Colorectal Carcinoma Cells by the Tyrosine Kinase Inhibitor STI571

Graziella Bellone, Dario Ferrero, Anna Carbone, Marlene R. De Quadros, Claudia Gramigni, Adriana Prati, Richard Davidson, Pierroberto Mioli, Luca Dughera, Giorgio Emanuelli and Ulrich Rodeck

Tyrosine kinase activation has long been known to be an important mechanism underlying tumor development, proliferation and local spread.¹ Inhibitors of these kinases have, therefore, been attractive targets of anti-cancer therapies.² The toxicity of non-selective tyrosine kinase inhibitors, however, has severely limited their use for clinical applications, leading to the search for “designer” inhibitors that selectively block specific groups of tyrosine kinases. By being more selective, these agents retain their anti-cancer activities while having a lower incidence of side effects. Perhaps the most promising agent that has emerged thus far has been STI-571 (a.k.a., Imatinib Mesylate, Gleevec[®]), while other tyrosine kinase inhibitors are at different stages of clinical trials.³

STI-571 is a low-molecular weight compound that binds to the phosphorylation pocket of specific tyrosine kinases. Initially designed to inhibit the oncogene *c-Abl*, STI-571 was also found to selectively inhibit *cKit* as well as *PDGFR α* and *PDGFR β* . Its first clinical application was in the treatment of chronic myelogenous leukemia (CML), where the translocation giving rise to the Philadelphia Chromosome results in a *Bcr-Abl* fusion protein that is a defining event during CML tumorigenesis. In early clinical trials, STI-571 has been shown to reliably induce remission in patients with CML.⁴⁻⁶ This early success led to other applications where mutations or chromosomal events involving one of the known targets are central events during tumorigenesis, such as the activation of *cKit* and *PDGFR* in gastrointestinal stromal tumors (GIST)⁷ and Dermatofibrosarcoma Protuberans (DFSP),⁸ respectively.

Apart from these selected tumors, upregulation of tyrosine kinases appears to be common in a broad range of tumors and helps to support tumor proliferation, even when activating mutations and chromosomal translocations are not present. This finding raises the question whether selective tyrosine kinase inhibitors may be equally effective in a broader range of human tumors. The paper presented by Bellone et al. provides some much needed insights into this issue. Using a colorectal carcinoma cell lines that expresses *cKit*, they demonstrate that exposure to STI-571 at concentrations as low as 5 μ M reduced cell viability and induced apoptosis. Interestingly, its efficacy was reduced with increasing amounts of fetal calf serum. When cultured in a Matrigel system, it also substantially diminished the ability of tumor cells to traverse barriers, suggesting that it could decrease local invasion through basement membranes. These effects are comparable to what they found in an earlier study when using a neutralizing antibody to *cKit*, leading them to conclude that STI-571's effect was mediated predominantly through *cKit* expression in the cell lines tested. They also corroborate similar findings by Attoub et al.⁹

These data are compelling at several levels. First, it supports the potential use of STI-571 as a chemotherapeutic and/or chemopreventive agent for colorectal carcinoma. Bellone et al. demonstrate that treatment with STI-571 also sensitizes cells to 5-FU, underscoring its potential as an adjunct to current chemotherapeutic regimens. It remains to be seen whether STI-571 will have similar anti-tumor activities in other forms of human cancer. Investigations into small cell lung cancer¹⁰ and pancreatic¹¹ cancer suggest that it is ineffective alone; however, it has not been studied in combination with other agents. The potential use of STI-571 outside of CML, GIST tumors and DFSP is unclear, although the current study supplies robust support for its use in colorectal cancer.

Second, this study demonstrates how selective inhibitors can be used to identify critical pathways involved in tumor development and/or demise. The authors propose that STI-571-induced apoptosis occurs through down-regulation of *Bcl-2* and upregulation of *Bcl-x_s*. From a mechanistic standpoint, therefore, STI-571 appears to impact on several critical signaling pathways in colorectal cancer. Our work with STI-571 in the colorectal cancer lines HCT116 and SW480 suggest that tyrosine kinase activation may regulate β -catenin signaling by disrupting the β -catenin/*E-cadherin* complex, thereby releasing free β -catenin into the cytoplasm.¹² Both HCT116 and SW480 have constitutively high levels of β -catenin due to activating mutations in *β -catenin* (i.e., *CTNNB1*) or loss-of-function mutations in *APC* respectively. In both cell lines, there was suppression of growth when exposed to STI-571,

even though they are not known to express cKit. Furthermore, the exposure of these cells to STI-571 substantially reduced Tcf4-driven expression of a luciferase reporter, indicating a disruption of β -catenin signaling. These data, combined with the findings from Bellone et al. suggest that the mechanisms underlying STI-571 may be significantly more complex than simple inhibition of c-Abl, cKit or PDGFr.

The study presented by Bellone et al. likely represents the first of many such studies into the use of “designer” tyrosine kinase inhibitors for cancer therapy. Although STI-571 can reliably induce remissions in CML, the remissions are often short-lived and resistance is common in recurrent tumors.^{6,13-16} Thus, while tyrosine kinase inhibition is promising in many respects, it is unlikely that these agents will represent “stand-alone” therapies. However, their use in combination with current chemotherapy may permit dose-reduction of highly toxic agents without compromising efficacy, and may reduce the occurrence of chemoresistance. Quite apart from the therapeutic benefit of these agents, selective tyrosine kinase inhibitors may represent extremely important tools to unravel the role of tyrosine kinase activation in tumor development. An enhanced understanding of the precise mechanisms behind tyrosine kinase regulation may, in turn, help to define strategies to improve efficacy and minimize resistance. In this respect, although STI-571 and other selective tyrosine kinase inhibitors are unlikely to represent wonder drugs on their own, they will play a vital role as adjuncts or synergistic agents in the treatment of a broad variety of human cancers.

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