Spotlight

By Gina Kirchweger

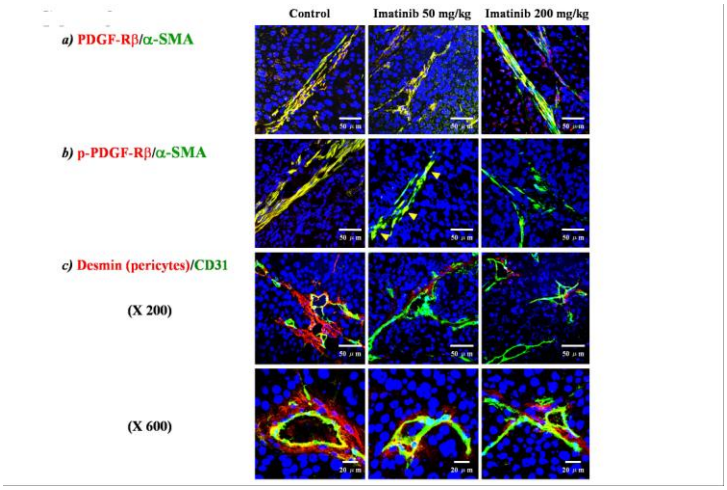
Imatinib for the Treatment of Gastrointestinal Tumors

Essat *et al*.
http://doi.wiley.com/10.1002/ijc.25827
Sumida *et al*.
http://doi.wiley.com/10.1002/ijc.25812

Over 90% of gastrointestinal stromal tumors (GIST) have a mutation in one of two receptor tyrosine kinases, the proto-oncogene KIT and the platelet-derived growth factor receptor alpha (PDGFRα). Until recently, surgery was the only treatment option available for GIST, which rarely responds to chemotherapy or radiation therapy. However, more than half of high-risk (tumor size > 10 cm or mitotic rate > 10/50 HPF) patients will develop recurrent disease within 2 years. Recently, oncologists started exploring the small-molecule tyrosine kinase inhibitor imatinib, which inactivates both KIT and PDGFRA, for the treatment of high-risk patients.

In this issue, Essat *et al*. systematically evaluated the clinical efficacy and safety of imatinib for adjuvant treatment of localized KIT-positive resected GIST. The only randomized controlled trial that met their eligibility criteria and included 713 people showed that recurrence-free survival after 1 year was significantly greater for the imatinib group than for placebo in adults with completely resected GIST (98% vs. 83%). These findings were supported by a number of observational studies.

In a related study, Sumida *et al.* examined the therapeutic effect of imatinib administered alone or in combination with irinotecan against human gastric carcinoma cells growing in an orthotopic nude mouse model. They focused mostly on tumor stroma, which, unlike tumor cells themselves, expresses PDGF-Rβ and has been shown to influence tumor progression. They found that blocking PDGF-Rβ signaling by oral administration of imatinib combined with intraperitoneal injection of irinotecan significantly inhibited not only the growth of tumors but also the incidences of lymph node and peritoneal metastasis.



Effects on imatinib on carcinoma-associated fibroblasts (CAF) and pericytes. Expression of PDGF-Rβ in CAFs did not change with treatment (a). Phosphorylation of PDGF-Rβ in CAFs was inhibited by treatment with imatinib. With low-dose (50mg/kg/day) imatinib treatment, p- PDGF-Rβ expression was not completely inhibited (yellow arrowhead), but the inhibition was marked by high-dose (200mg/kg/day) imatinib treatment (b). Endothelial cells were identified by green fluorescence, whereas pericytes were identified by red fluorescence (c).