



Pazopanib: a new therapeutic option for advanced gastrointestinal stromal tumors

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Gastrointestinal stromal tumors (GIST) are the most common mesenchymal malignancy of the alimentary tract, with an annual incidence of 6,000 new cases in the United States (1). Surgery has been the mainstay of treatment for GIST, but a significant number of patients develop unresectable or metastatic disease. Since most GISTs are driven by constitutively active receptor tyrosine kinases (KIT in 85% and PDGFRA in 10%) (2,3), systemic therapy for advanced GIST consists primarily of tyrosine kinase inhibitors (TKIs). Imatinib, a multi-targeted TKI with activity against KIT and PDGFRA, was the first of these to show significant efficacy against unresectable or metastatic GIST, with a median progression-free survival (PFS) of 24 months (4). However, over 80% of patients eventually develop imatinib resistance. Sunitinib, another multi-targeted TKI, was shown to confer a median PFS of 24 weeks for imatinib-resistant/intolerant patients (5), and it has now become the second-line therapy for advanced GIST. Unfortunately, almost all of these patients also subsequently develop sunitinib resistance over time.

A phase 2 randomized study by Mir and colleagues, the PAZOGIST trial, was recently published in *The Lancet Oncology* and demonstrated that pazopanib, a multi-targeted TKI with activity against KIT, PDGFRA, and VEGFR, improved PFS in patients with locally advanced or metastatic GIST resistant to both imatinib and sunitinib. PAZOGIST enrolled 81 patients, 40 of whom were randomized to receive pazopanib plus best supportive care, and the remaining 41 of whom were randomized to best supportive care only, but with the opportunity to receive pazopanib upon disease

progression. Median PFS was 3.4 months in the pazopanib group compared to 2.3 months in the control group ($P=0.03$). Median PFS in the control group who received pazopanib after progression ($n=36$) was 3.5 months from initiation of pazopanib. All patients who did not progress on pazopanib had stable disease, as there were no partial or complete radiographic responses. Overall survival could not be compared, since patients in the control group were allowed to cross over and receive pazopanib after progression.

The most commonly reported side effects of pazopanib were hypertension, fatigue, and diarrhea, and three grade 5 complications (2 pulmonary emboli and 1 hepatic failure) were noted. These adverse reactions are comparable to those of patients on other TKIs, and also to those of patients taking pazopanib for metastatic renal cell carcinoma or soft tissue sarcoma, for which it is FDA-approved. Of note, pazopanib requires an acidic environment with pH less than 4.0 for solubility, and the authors noted a decreased plasma concentration of pazopanib in patients who had previously undergone total gastrectomy. However, gastrectomy-related decreased bioavailability was not definitively shown to negatively correlate with tumor response.

Currently, advanced GIST is treated with imatinib as first-line therapy, sunitinib as second-line therapy, and now regorafenib as third-line therapy. Regorafenib, a novel multi-targeted TKI, was shown in a phase 3 trial to produce a median PFS of 4.8 months in imatinib- and sunitinib-resistant patients (6). It was subsequently approved for use in GIST patients by the FDA and became the standard-of-care third-line agent while the PAZOGIST trial was still

ongoing.

Another TKI that has been evaluated for third-line therapy against advanced GIST is nilotinib. Nilotinib was shown in a phase 2 trial to produce a median PFS of 118 days in imatinib- and sunitinib-resistant patients (7). Like pazopanib, bioavailability of nilotinib was reduced in patients who had undergone prior gastrectomy (8). Both regorafenib and nilotinib, like pazopanib, are also primarily disease stabilizing, as there were no complete responses in any of these trials, and partial response rates for regorafenib and nilotinib were 4.5% and 3%, respectively.

Pazopanib falls within the existing paradigm of using one TKI until resistance develops, then switching to another TKI with a potentially broader range of receptor targets. Thus, it produces similar diminishing PFS returns as the other third- and fourth-line agents. However, the improvement in progression-free survival with pazopanib was modest (3.4 *vs.* 2.3 months) but significant in this patient population with resistant disease who had failed both first- and second-line therapy. The superiority of pazopanib to best supportive care makes it a promising new addition to the existing lineup of multi-targeted TKIs used to treat advanced GIST.

A potential alternative strategy being explored for advanced GIST involves selecting particular TKIs based on specific mutations that a particular tumor harbors. PAZOGIST attempted to address this hypothesis with an exploratory analysis that stratified response to pazopanib with specific mutations in KIT (exons 9, 11, 13, or 17) and PDGFRA (exons 12, 14, or 18). While the authors noted a potential association between KIT exon 11 mutation and response to pazopanib, they acknowledge that their sample size was not adequate to draw definitive conclusions. The nilotinib study was similarly underpowered to detect any statistically significant association between specific mutation status and response to a particular TKI.

Advanced GIST continues to pose a significant therapeutic challenge as these patients become more and more resistant to multiple TKIs over time. Mir and colleagues have demonstrated that pazopanib is a novel multi-targeted TKI that can be used in patients with imatinib- and sunitinib-resistant GIST with comparable results to other third- and fourth-line agents, adding another agent to the existing TKI arsenal. However, further studies are necessary to better elucidate the molecular mechanisms of TKI resistance, as this could subsequently allow for genetic biomarkers to be used to select for and predict response to specific TKIs and more appropriately

tailor therapy for each individual patient. Ultimately, as tumors become increasingly TKI-resistant, other targets beyond KIT and PDGFRA will need to be discovered in order to make further progress. The eventual goal would be to develop combination therapies for advanced GIST that simultaneously target multiple resistance pathways.

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Footnote

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References

1. Ma GL, Murphy JD, Martinez ME, et al. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev* 2015;24:298-302.
2. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors.

- Science 2003;299:708-10.
3. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998;279:577-80.
 4. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard-versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 2008;26:620-5.
 5. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;368:1329-38.
 6. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381:295-302.
 7. Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. *Cancer* 2011;117:4633-41.
 8. Kim KP, Ryu MH, Yoo C, et al. Nilotinib in patients with GIST who failed imatinib and sunitinib: importance of prior surgery on drug bioavailability. *Cancer Chemother Pharmacol* 2011;68:285-91.

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