Commentary

Treatment of refractory gastrointestinal stromal tumor using pazopanib

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Gastrointestinal stromal tumor (GIST) is the most common sarcoma in the gastrointestinal tract. Its incidence rate is 1–1.5 per 100,000 per year (1), consistent to the worldwide incidence of approximately 10–20 million people per year (2). Although GIST is generally resistant to both radiation therapy and chemotherapy, over the last two decades GIST has become one of the most controllable sarcoma by molecularly targeted therapies (3). Most GIST express aberrantly activated transmembrane tyrosine kinase (TK) receptors, either KIT or PDGRFA (4). KIT mutation accounts for 80% of GISTs and is most common in exon 11 (65%) followed by exon 9 (8%) (1,2). PDGFRA mutation accounts for less than 10% of cases. GIST without identifiable KIT or PDGFRA mutations are collectively called wild-type and account for 10–15% of patients (5).

Tyrosine kinase inhibitors (TKI) have been extremely successful in the treatment of GIST having KIT mutations. In the metastatic setting, multiple lines of therapy are available including imitanib (first line), sunitinib (second line), and regorafenib (third line) (6). Adjuvant imatinib has significantly improved the recurrence-free survival of patients with GISTs (7,8). However, the development of imatinib resistance is a major challenge in GIST treatment. Patients on imatinib sometimes develop secondary KIT mutations conferring resistant to imatinib. Although sunitnib can sometimes be effective in the second line of treatment, patients will ultimately become resistant to sunitinib as well (9,10). In patients who have progressed on imatinib and sunitinib, regorafenib was shown to significantly improve progression-free survival (PFS) compared with placebo (11) leading to FDA approval for advanced GIST. A number of agents have been tested in subsequent lines of therapy including panopanib (4,12), sorafenib (13), nilotinib (14).

In the recent *Lancet* article (12), Dr. Olivier Mir and fellow colleagues published the results of a randomized, multicenter, open-label phase 2 clinical trial of pazopanib in patients with known resistance to imatinib and sunitinib. Pazopanib is a multitargeted TKI which inhibits KIT, PDGFR, and has particularly potent activity of VEGFR (4). A total of 81 patients were enrolled in the clinical trial from April 12, 2011 to December 9, 2013. Advanced GIST patients were stratified by the number of treatments (2 *vs.* ≥3), then randomly assigned to two groups—pazopanib plus the best supportive care (PBSC) (40 patients) or the best supportive care (BSC) alone (41 patients). Patients were assessed at week 4, 10, and 16 and then every 8 weeks until treatment discontinuation. The primary endpoint was PFS based on both the investigator-assessed progression and centrally assessed progression. Results demonstrated that the centrally assessed 4-month PFS rate was significantly longer in the PBSC at 44.3% (95% confidence interval of 28.1–59.3%) compared to the survival rate of BSC at 17.6% (95% confidence interval of 7.8–30.8%). The investigator-assessed 4-month PFS showed consistent results. Median investigator-assessed PFS is 3.4 months (95% CI of 2.4–5.6) in the PBSC and 2.3 months (95% CI of 2.1–3.3) in the BSC [hazard ratio (HR) 0.59 (95% CI of 0.37–0.96)]. A trend towards improved overall survival was not statistically significant. The authors concluded that pazopanib had significant effect in controlling activity

of GIST after resistant to imitanib and sunitanib. This result contrasts with the marginal activity of pazopanib for advanced GIST after resistant to imitanib and sunitanib reported by a separate study published by Ganjoo *et al*. in 2014 (4). One potentially contributory factor noted by the current study is that patients with a prior history of gastrectomy or with the PDGRFA mutation do not significantly benefit from pazopanib. Prior gastrectomy may be associated with increased gastrointestinal pH levels leading to decreased efficacy of pazopanib. Patients with PDGRFA mutation may be less responsive to pazopanib. These categorizations were not defined in the study by Ganjoo *et al*. The lower efficacy found in their study could be due to the potential higher percentage of participants in these two groups. The lower number of participants, only 25 patients, in the prior study, also likely contributed to the non-significant result.

One important note is that results in Mir *et al*.'s study patients did not receive regorafenib, which is now typically given as the third line treatment for most advanced GIST patients after imitanib and sunitanib resistance in the United States and therefore further study on the efficacy in the modern refractory population is still warranted. Patients with refractory GIST have several options including sorafenib (13) and nilotinib (14). This randomized trial, now establishes pazopanib as a particularly important option for patients with refractory GIST.

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Footnote

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