Editorial

A new promising quinazoline-derived Pan-KIT mutant inhibitor for the gastrointestinal stromal tumors (GIST) management

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors commonly located in stomach (60%) and small intestine (25%), but they can also be found in other parts of the gastrointestinal tract (1). GISTs are characterized by hotspot mutations in *KIT* and *PDGFRA* oncogenes. These oncogenes codify type III receptor tyrosine kinase which, after binding to the ligand [stem cell factor (SCF) and platelet-derived growth factor (PDGF), respectively], results in receptor homodimerization and kinase activation (2,3). The presence of activating mutations of *KIT* and *PDGFRA* causes ligand-independent kinase and downstream signaling pathways activation, including MAPK, PI3k/AKT, and STAT3 pathways (1,4).

Approximately 80% of GISTs harbor *KIT* mutations, including in-frame deletions, insertions, substitutions, or combinations thereof (1,2). Most mutations affect the juxtamembrane (JM) domain, encoded by exon 11, and disrupt the normal juxtamembrane secondary structure responsible for maintaining the KIT inactive conformation (1,2). Importantly, shorter progression-free and overall survivals are associated with deletions when compared with the other exon 11 mutations (1,5). Specifically, deletions in codons 557 and/or 558 are related to malignant behavior (1,5). In addition to exon 11 mutations, about 10% of *KIT* mutations occur in exon 9, followed by exon 17 and exon 13, that occur in a very low percentage (1). In about 10% of cases, mutations in the PDGFRA are found and often associated with low-risk GIST (4). PDGFRA is activated in GISTs with mutations specially in exon 18, followed by mutations in exon 12 and 14 that are rarer (2). In a subset of 10% KIT/PDGFRA wild-type GIST, somatic *BRAF* mutations and germinative *SDHx* mutations are described (2,6)

In 2002, the tyrosine kinase inhibitor (TKI) imatinib was FDA-approved as first-line treatment for GIST patients (1,2,5). Imatinib inhibits KIT kinase by directly binding to the ATP pocket and competitively inhibiting the ATP binding. Additionally, PDGFRA, ABL, FLT3 (Fms-like tyrosine kinase 3), and CSF1R (macrophage colony-stimulating-factor receptor) are also imatinib key molecular targets (5). Despite the imatinib efficacy, it is known that about 10% of patients have primary resistance (tumor progression within the first 6 months of treatment) specially in cases with D842V *PDGFRA* mutation, followed by wild-type and, exon 9-mutant KIT (1). In addition, most of the patients will develop secondary resistance (within two years) due to new, or secondary, mutation in *KIT* or *PDGFRA* (1).

Most GIST patients who develop secondary resistance to imatinib are treated with another TKI, sunitinib, as second line therapy. Sunitinib received FDA approval in 2006 and

targets KIT, PDGFRA, VEGFR and RET receptors (5). Nevertheless, its activity against secondary imatinib-resistant kinase mutations was shown to be suboptimal resulting in a progression-free survival of approximately 6.5 months (5,7). Most recently, regorafenib, another generation of TKI, was approved by the FDA as third line therapy, targeting KIT, PDGFRA, RET, RAF1, BRAF, VEGFR 1–3, and FGFR receptors (5,7). Several alternative TKIs as nilotinib, masatinib, sorafenib, dovitinib, pazopanib, and others have been studied in GIST resistant cases, but so far have shown disappointing results (8).

In a recent publication, Kettle and co-authors reported a new promising quinazoline-derived pan-KIT mutant inhibitor for GIST treatment (9). To identify this novel inhibitor, the authors optimized an existing kinase scaffold from several phenoxyquinazoline and quinoline structures related to TKI inhibitors previously described (9). They identified AZD3229, a multitargeted agent able to promote growth inhibition of a series of mutant KIT-Ba/F3 derived cell lines, with good margin to KDR (VEGFR2)-driven effects and kinome selectivity presenting the same performance as other successful approved GIST agents (9).

Quinazolines moieties are noteworthy in medicinal chemistry due to the wide range of biological properties (10). These compounds were found to be inhibitors of not only EGFR [e.g., gefitinib (Iressa®)], but many other tyrosine kinase receptors as well (11). Several studies of the quinazolinone ring structure activity revealed that substituents at different positions could improve antimicrobial activities (12). Moreover, a dimethoxyquinazoline, known as prazosin, belongs to the class of alpha-adrenergic blockers and is used to treat high blood pressure (13). This point should be highlighted, considering that hypertension consists of one of the most common side effects of TKIs, resulting particularly from the KDR inhibition. Thus, these studies greatly extend the knowledge for quinazolines biological importance such as anticancer and antihypertensive activities and provide a basis for new potential therapeutic targets.

Kettle's group demonstrated that AZD3229, through C7 methoxyethoxy group modification, compared to others compounds with different substituents at quinazolinone ring positions tested, have a great equilibrium between *KIT* mutant potency and KDR selectivity able to limit the hypertension potential frequently seen in GIST therapies (9). Therefore, these substitutions show significant improvements in physicochemical and ADME (absorption, distribution, metabolism, and excretion) properties (9).

Kettle and colleagues also evaluated the broad *KIT* mutant inhibition profile compared to current standard clinical agents (imatinib, sunitinib, and regorafenib) and agents in clinical trials [ripretinib (DCC-2618) and avapritinib (BLU-285)] and assessed an extended panel of human kinase binding assays through general kinome selectivity (9). Interestingly, AZD3229 presented a broad selectivity suchlike as observed for imatinib and avapritinib, presenting lower amplitude of inhibition. As expected for multitargeted kinases, both sunitinib and regorafenib showed a greater activity across the panel, and ripretinib presented an intermediate activity spectrum. These evidences open up a wider profile of AZD3229 potential (9). However, it must be taken into account that even though many patients tolerate TKIs better than cytotoxic chemotherapy, they could develop adverse effects arising from on-target and off-target effects (14). Therefore, particularly in GISTs, benefits have been associated with drug-dependent off-target effects, such as modulation of immune responses, and angiogenesis (15). Thus, a complete characterization of on-target and off-target effects as well as the elucidation of the mechanisms of action may be required from complementary approaches.

Finally, the authors also showed *in vivo* efficacy of AZD3229 compared to imatinib, sunitinib and regorafenib of relevance to each mutant using Ba/F3 cell lines (9). They showed that AZD3229 at a dose of 20 mg/kg b.i.d induces tumor volume regression more effectively than regorafenib at a dose of 100 mg/kg q.d and imatinib. On the other hand, in an exon 11 del/V654A allograft AZD3229 at a dose of 2 and 20 mg/kg b.i.d induces tumor volume regression. Sunitinib, revealed great regressions at 80 mg/kg q.d as expected with its clinical practice experience and when compared to AZD3229 at a dose of 20 mg/kg b.i.d (9). Although Kettle's group provides important evidence of AZD3229 efficacy *in vivo*, its clinical application still has a long way to go. Voskoglou-Nomikos and colleagues reported that the clinical translatability of models containing murine allograft is frequently poor compared to human cell models (16). Thus, despite differences of *in vivo* models, each offers vulnerabilities as well as advantages and disadvantages and may be addressed by these findings in other models like patient-derived models of acquired resistance that can better recapitulate the original patient-tumor complexity (17).

In conclusion, the results published by Kettle and

colleagues are exciting and suggest that a structure-based design of quinazoline derived pan-KIT mutant inhibitor is promising. Now, a refined clinical application of this inhibitor is needed, using other robust *in vivo* models as well as to define on-targets and off-targets activities, in order to provide maximal impact in cancer treatment and provide patients with the greatest chance of valuable benefit.

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