Editorial

Gastrointestinal stromal tumors—are we stuck and the way forward

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Casali *et al.* recently published the much-awaited long-term results of the Euro-Australasian phase III randomized trial comparing standard dose of 400 mg imatinib daily with a higher dose of 400 mg twice daily in patients with advanced or metastatic gastrointestinal stromal tumors (GIST) (1). In summary, the study indicated that there is a small subset of patients who are long-term survivors and that a lower tumor burden might predict better survival (1). These results can serve as a guiding torch towards future research to improve our present understanding and management of GIST.

Identifying and understanding this subset of long-term survivors is an unfinished task. It might be possible that these patients are the subset with very low tumor burden or, as mentioned by the authors, just the tail of the random Gaussian distribution. An increased tumor load may lead to increased chances of multiple mutated, resistant clones leading to poor progression-free survival and overall survival. The authors correctly concluded that with regards to the trial outcomes, there is lack of any difference between the two arms in terms of median progression-free survival, overall survival, and response rate (1). The study also reported benefit in progression-free survival with high-dose imatinib in patients with exon 9 mutated GIST and modest benefit with escalating to 800 mg on progression at lower dose (1). The weakness of the trial lies in the timing of its commencement, which lacked advanced testing like next-generation sequencing, liquid biopsies, circulating tumor DNA sequencing, primary and secondary mutations analysis which might have helped in better stratification of the subsets and understanding of resistance mechanisms. However, whether such a trial will be possible now is doubtful considering imatinib is off-patent and the parent drug company Novartis might lack the incentives to run such a trial. Moreover, the research focus is now gearing towards targeting specific mutations like phase III study of crenolanib in imatinib-resistant D842V mutation (2) or testing novel tyrosine kinase inhibitors, biological inhibitors of KIT and PDGFRA (olaratumab), HSP90 inhibitors, FGFR inhibitors, glutaminase inhibitors, immunotherapies, insulin-like growth factor pathway inhibitors, inhibitors of downstream pathways of KIT and PDGFRA (BRAF, MEK, PI3P, AKT, mTOR) or other cell cycle inhibitors (alvocidib, palbociclib) in treating GIST (2-4).

Till the late 1990s, GISTs were being misclassified as smooth muscle tumors such as leiomyomas and leiomyosarcomas. With the discovery of CD34 immunopositivity and later on near-universal expression of CD117 (KIT) by immunohistochemistry followed by anoctamin-1 (ANO1 or DOG1) provided the much-needed diagnostic tools (2,5). Thereafter rapid strides in understanding epidemiology, pathology, molecular genetics, and treatment were made in GIST. GISTs now

undergo mutational analysis for KIT, PDGFRA, succinate dehydrogenase (SDH), and BRAF testing prior to being classified as quadruple negative, which itself may harbor mutations like NF1 (6). With regards to treatment imatinib, sunitinib, and regorafenib are approved for treatment of advanced GIST. Imatinib remains the cornerstone of management in patients with targetable mutation (7). Other tyrosine kinase inhibitors such as sorafenib, nilotinib, dasatinib, and pazopanib have been studied in smaller studies and may have some modest effect. Enrollment in clinical trials remains the best strategy in advanced GIST (7).

The incidence of GIST is increasing annually (8); this may be due to improvement in immunohistochemistry and molecular classification, increased diagnosis of incidental GISTs on imaging, surgeries and endoscopies for unrelated purposes (9), or due to factors currently unknown to us. Though imatinib revolutionized the treatment and is the poster child for success stories of tyrosine kinase inhibitors in GIST, we now know that its long-term effectiveness is limited to less than 10% of patients (1). Few patients with imatinib treatment demonstrate primary resistance (disease progression within first 6 months of therapy), and at least half of the patients develop secondary resistance within 2 years (10). Also, many patients are unable to tolerate imatinib due to toxicities. Imatinib is not effective in patients with resistant mutations (such as in PDGFRA exon 18 D842V) as well as in wild-type (for example SDH-deficient, NF1- or BRAF-related) GIST (11). Therefore, the number of patients needing effective therapy after or apart from imatinib continues to rise, and not much is known about how to treat them. Even in patients who undergo long-term disease control, the treatment duration for which imatinib needs to be continued is unclear.

Casali *et al.* reported that most of the patients in the trial who remained progression-free after 10 years continued to be on imatinib (1). Though imatinib can be safely discontinued in many patients with chronic myelogenous leukemia with deep molecular response for at least 2 years (12), similar data in long-term GIST survivors is lacking. Earlier results from the BFR 14 trial has shown that imatinib interruption after 1, 3, or 5 years of treatment in patients with non-progressive GIST was associated with disease progression, even in patients with complete response. Moreover, though reinitiating imatinib restored tumor control and didn't affect overall survival, the quality of responses were inferior as compared to those prior to discontinuation (13). Therefore, there is a need for some kind of biomarker like major molecular response in GIST to identify the subset of patients in whom imatinib can be safely discontinued.

As discussed, while the discovery of KIT and PDGFR as drug targets changed the landscape of GIST treatment, it came with certain pitfalls. The easy and effective treatment of GIST by tyrosine kinase inhibitors leads to their use as frontline treatment in the community setting, which indirectly served as a roadblock because fewer patients were referred for clinical trials at high-volume centers. The field, therefore, grew at a lesser pace as it is hard to do big studies on GIST not only due to their rarity but also because of less referral due to effective front-line therapies. In research to the focus was more on targeting the same tyrosine kinase pathway with inhibitors as compared to exploring other potential pathways such as combining targeted therapy with immunotherapy (4,14), exploiting unique metabolic deficiencies like loss of expression of argininosuccinate synthetase 1 (2), modulating tumor microenvironment and epigenetics, and targeting KIT by alternative ways like engaging switch pocket technology or tweaking its stability (15).

It might also be worthwhile revisiting chemotherapy and radiation therapy in this new era. Traditionally GISTs are considered to be refractory to both radiation and chemotherapy (16). But this is based on old studies from the pre-imatinib era when both these modalities were being hammered by GISTs. However, now we know that chemotherapy and radiation both can modulate the tumor microenvironment and immune system (17) and may boost response to targeted therapies. Another option that seems intriguing is tumor debulking. Casali *et al.* reported that a small number of patients in the study underwent surgery for residual disease (1), but drawing a conclusion might not be possible due to small numbers, unplanned procedure per protocol, and selection bias. But we now know that 90% of patients will fail imatinib in the long run, and whether decreasing tumor burden may delay the onset of subsequent resistance is a matter of debate (18).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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