Editorial

Modern times call for modernized treatment strategies for advanced gastrointestinal stromal tumors

Shruthi R. Perati^, Andrew M. Blakely^

Surgical Oncology Program, National Cancer Institute/National Institutes of Health, Bethesda, MD, USA

Correspondence to: Shruthi R. Perati, MD. Surgical Oncology Program, National Cancer Institute/National Institutes of Health, NIH Clinical Center, 10 Center Dr., Bethesda, MD 20892, USA. Email: shruthi.perati@nih.gov.

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Over the last 25 years, molecular profiling of and systemic treatment options for gastrointestinal stromal tumor (GIST) have greatly expanded. In the modern era of increasingly personalized medicine, there remains a need for improved understanding of how to best tailor these management options to individual patients in order to achieve maximum treatment benefit. In this issue of the *Journal of Gastrointestinal Oncology*, Li *et al.* share their institutional retrospective analysis of clinical characteristics independently associated with survival in patients with advanced GIST (1). The authors included patients with primary unresectable or recurrent GISTs, comprising the patient population that arguably stands to most benefit from new tyrosine kinase inhibitor (TKI) therapies, over a contemporary period [2010–2023]. Of note, all patients in this study had received TKI therapy, and the majority of patients had received multiple lines of treatment. Li *et al.* were able to capture patients treated following regulatory approval of sunitinib [2006] and regorafenib [2013], as well as more recently ripretinib and avapritinib [2020]. The authors demonstrated that the following factors were associated with improved overall survival: lower tumor burden, liver-only metastasis, and being TKI-treatment naïve.

Li *et al.* highlight the prognostic factors for advanced GIST patients on TKI therapy; however, there is still room to translate this into more personalized TKI selection on a case-by-case basis. Despite novel TKI therapies becoming available during this study period, overall survival outcomes changed only marginally, suggesting that simply having more tools is ineffective without appropriate matching of these therapies to patients' specific tumor molecular profile and biology. To illustrate this point, Li *et al.* demonstrate that patients who developed recurrence during imatinib treatment had a median PFS (mPFS) of 9.1 months. This is only marginally worse than their reported mPFS for sunitinib (9.7 months), and non-superior to the mPFS of ripretinib (9.1 months), famitinib (5.3 months), and anlotinib (1.8 months).

Avapritinib is the only TKI in this study with significantly greater mPFS than patients with recurrence after withdrawal from, or while on, imatinib therapy. Given that avapritinib is used as a first-line treatment option for PDGFRA D842V mutant GISTs, it is unsurprising that it has demonstrated much greater survival benefit (2).

Ripretinib has also emerged as a TKI therapy with a broad inhibitory profile, with efficacy against *KIT* exon 13, 14, 17 and 18 mutations (3,4). While ripretinib has been used clinically for GISTs that have developed secondary resistance to imatinib, it is possible that these presumed "secondary mutations" have been present since the time of diagnosis.

These examples of both avapritinib and ripretinib

^ ORCID: Shruthi R. Perati, 0000-0003-1576-1032; Andrew M. Blakely, 0000-0002-5013-3851.

underscore the importance of routine, early molecular profiling of GIST biopsies/specimens through genotyping whenever possible. In addition, SDHB immunohistochemical staining should be done to identify wild-type GISTs, to avoid starting imatinib in the first place and more carefully consider the relative benefit of sunitinib or regorafenib (5). These efforts will serve to maximize the chances of treatment response while concomitantly minimizing the potential adverse effect of mixed-action TKI therapies that may be inherently ineffective for an individual patient. For instance, if a patient's tumor molecular testing demonstrated an exon 11 and secondary exon 13 (or 17) mutation, oncologists should consider promptly starting treatment on ripretinib, perhaps after a short course of imatinib treatment. To that end, the INSIGHT trial is a randomized study of ripretinib *vs.* sunitinib in advanced GIST patients and applies this nuanced mutation-specific approach, with inclusion criteria accounting for co-occurring *KIT* exon 11 with exon 17 or 18 mutations (without exon 9, 13, or 14 mutations) (6). Ripretinib has also been shown to demonstrate improved tolerability as compared to sunitinib (7), further supporting that traditionally later-line therapies should potentially be administered earlier in treatment paradigms. Combination therapies may also benefit patients with multiple non-exon 11 mutations; the Peak trial is one such study that has demonstrated an acceptable safety profile using the combination of bezuclastinib and sunitinib to target both more common *KIT* primary mutations (exons 9 and 11), as well as secondary mutations (exons 13, 14, 17, 18) (8).

Optimized utilization of TKI therapy options tailored to individual patients' GIST genotypes may ultimately increase the odds of achieving stable or responsive and therefore potentially resectable disease (9). Reaching that point before patients have either accumulated too many irreversible adverse effects of treatment or have developed widespread metastatic disease may improve their survival. Multidisciplinary care should be implemented as early as possible in a patient's care in order to jointly identify the best opportunity for resection and potentially provide a TKI treatment break for the patient. To this end, adjuvant treatment strategies should also be enhanced as newer TKI agents are added to our armamentarium.

In summary, the management of patients with advanced GIST is challenging, due to acquired and often clonal resistance to TKI therapy. Given the heterogeneity of driver mutations in GIST, it is imperative that all patients undergo tumor molecular profiling to identify the most appropriate first-line and subsequent therapy. The findings and conclusions from longitudinal retrospective studies such as the one by Li *et al.* and ongoing clinical trials such as the INSIGHT and Peak studies should be considered when designing future randomized controlled trials in order to identify optimal treatment sequencing of established agents, new agents, and combinations thereof for patients based on their tumor profiles. Ultimately, careful clinical trial design and their respective findings will prompt regulatory bodies to update their treatment paradigms for GIST and approve the use of modern TKIs in the second or even first line. Ideally, this approach will translate to improved patient outcomes.

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