Editorial Commentary

Advancing the promises of precision medicine for patients with gastrointestinal stromal tumor

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Comment on: Bartholomew AJ, Dohnalek H, Prins PA, *et al.* Underuse of exon mutational analysis for gastrointestinal stromal tumors. J Surg Res 2018;231:43-8.

Received: 01 February 2019; Accepted: 15 March 2019; Published: 04 December 2019.

doi: 10.21037/gist.2019.10.01

View this article at: http://dx.doi.org/10.21037/gist.2019.10.01

Gastrointestinal stromal tumor (GIST) treatment is one of the best examples of how precision medicine can impact outcomes in patients with cancer. In 1998, Hirota and colleagues reported that GISTs carried gain-of-function mutations in the proto-oncogene, *c-KIT* (1). Although considered a rare malignancy, GIST is the most common mesenchymal neoplasm of the gastrointestinal tract (2-4). GIST is the model of molecularly driven malignancy characterized primarily by the presence of activating mutations in c-*KIT*, the normal cellular homologue of the viral oncoprotein v-Kit (v-Kit, Hardy Zuckerman 4 feline sarcoma viral oncogene homologue) (5,6) or *PDGFRA* (platelet derived growth factor alpha). The extraordinary evolution of the treatment landscape of this disease dates to the discovery of the CD117 antigen, the product of the c-KIT oncogene identified in almost all GISTs but not in other mesenchymal tumors (5,6). Before this, there was no effective therapy for patients with advanced GIST. The development of imatinib mesylate (also known as Gleevec™) (7), an oral 2-phenylaminopyrimidine derivative that works as a selective inhibitor against mutant forms of type III tyrosine kinases such as BCR/ABL, KIT, and PDGFRA (8), revolutionized the treatment for patient with GIST. Imatinib was originally approved for chronic myelogenous leukemia but in a proof of concept trial, a dramatic, rapid, and sustained response in a patient with GIST treated with imatinib was observed and further studies resulted in the regulatory approval of imatinib for metastatic disease and adjuvant therapy. Extensive mutational studies over the past decade have found that the majority of GISTs carry a *KIT* or *PDGFRA* mutation (9,10). However, in about 10% of adult GISTs and 80% of pediatric tumors, neither a *KIT* nor a *PDGFRA* mutation is found. These tumors were originally referred to as "wild-type" GISTs, but subsequent study found *SDHA/B/C/D* mutations, *SDHC* promoter hypermethylation, or mutations in *NF1* and *BRAF* as well as other rare mutations/fusions such as *NTRK* (11-13).

Mutational analysis in *KIT* and *PDGFRA* provides prognostic and predictive value in the management of GIST. Current guidelines from the National Comprehensive Cancer Network (NCCN) strongly recommend testing for mutations in *KIT* and *PDGFRA* in GIST patients if medical treatment is planned. It is also recommended that patients with GISTs lacking detectable mutations in *KIT* or *PDGFRA*, be tested for SDHB by immunohistochemistry and if deficient (SDH-deficient GIST) these patients be referred for germline testing of *SDH* genes. Despite this, the use of mutational analysis in GIST has not been universally followed by treating physicians. In the paper by Bartholomew *et al.* (14), the authors report on the results of their study aimed to better define the practice pattern in the use of exon mutation analysis (EMA) per NCCN guidelines and its impact in GIST patients receiving a tyrosine kinase inhibitor (TKI) therapy at a comprehensive cancer center. The records of 104 patients receiving TKI between 2006 and 2017 were analyzed. Thirteen gastrointestinal medical oncologists from 10 hospitals within the MedStar

Georgetown Cancer Institute were administered a questionnaire to assess EMA perception and awareness of NCCN guidelines pertaining to EMA testing in the management of GIST. Fifty-four of the 104 patients (52%) received TKI but of these, only 41% had any form of genotyping. Among patients who had EMA, 59% continued the original TKI, 32% were changed to another TKI, and 9% discontinued or no TKI was used. Although almost all physicians felt that EMA is a valuable tool, only 62% of them used EMA "frequently" or "always" to guide their decision in treatment recommendations. One telling observation is the lack of increased use of EMA between 2006–2011 as compared to 2012–2017, even as more scientific studies demonstrate the benefit for genotyping.

The authors suggest that NCCN guidelines advocate for EMA testing in all patients undergoing TKI therapy. This is now included in the current guidelines. They also propose further cost benefit analysis of the use of EMA. Finally, the major question for follow-up is whether or not EMA improves overall survival outcomes in GIST patients.

GIST has become a paradigm of molecular diagnostic test with majority harboring gain-of-function mutations in *KIT* or *PDGFRA* genes. Determining the molecular sub-classification of GIST informs appropriate management of GIST. Primary and secondary mutations can cause therapeutic resistance. The *PDGFRA* D842V mutation is the most common *PDGFRA* mutation found in 5% to 6% of primary GIST. These tumors are more resistant to imatinib and to most TKIs. Other causes of drug resistance to imatinib include mutations of exon 17, 18, and 13. The prevalence of these mutations increases with subsequent lines of therapy, particularly, those involving the activation loop.

Prior to more widespread genotyping of GIST, Frolov and colleagues in 2003 were the first to identify genetic markers that could potentially predict a priori the response of patients with metastatic GIST to imatinib using clinical trial samples (15). Using earlier gene expression platforms and bioinformatic tools, we evaluate clinical specimens obtained before and after imatinib therapy from patients enrolled on the CSTI571-B2222 clinical trial. This Phase II clinical trial was one of the first to evaluate the efficacy of imatinib in unresectable or metastatic GISTs expressing c-KIT. Although there were no complete responses, 88% and 78% of patients were alive at 1 year and 2 years, respectively while on imatinib (either 400 or 600 mg/day). In our study, we found gene expression patterns that were predictive of likely response to imatinib, including significant down-regulation of *ARHGEF2*, *FLJ20898*, *FZD8*, *PDE2A*, *RTP801*, and *SPRY4A*, and upregulation of *MAFbx* (15). Our recent studies of GIST and molecular markers of response to imatinib have found that one of the top predictive tissue-based biomarkers, SPRY4, can also be found in the blood of GIST patients, *i.e.*, as part of the molecular cargo of small extracellular vesicles (EVs), also referred to as exosomes. We have shown through unbiased proteomic studies that SPRY4 as well ALIX, PDE2A, and SURF4, are present in circulation exosomes from GIST patients and their relative levels are associated with response to imatinib therapy (16). Furthermore, we demonstrated that the circulating levels of exosome-associated KIT (both total, exoKIT and phosphorylated, exop-KIT^{Tyr719}) and exoSPRY4 decrease significantly in patients with primary GIST after treatment while the levels increased substantially in metastatic GIST patients following disease progression while on imatinib therapy. These studies suggest that circulating levels of small EVs and their molecular cargo can be used to develop liquid-based biopsies for the diagnosis, prognosis, and monitoring of response to treatment of these tumors.

After imatinib failure, the magnitude of benefit from subsequent therapy with other TKIs has not always been satisfactory without further molecular information. Some use the empiric approach of continuing imatinib at a higher dose or use other TKIs like sunitinib and regorafenib. Non-approved TKIs such as nilotinib, pazopanib, dasatinib and sorafenib may be considered as a "bridge" until a clinical trial becomes available for the patient. It is unlikely that sorafenib will work in the setting of progression from regorafenib. Pazopanib may be appropriate for GIST lacking a KIT mutation. Dasatinib is also a reasonable option for GIST patients lacking somatic mutations as well as those with *PDGFRA* D842V mutation.

The development of newer generation TKIs are underway. Avapritinib, formerly known as BLU-285, is a highly potent and selective inhibitor of GISTs with *KIT* and *PDGFRA* mutations. Avapritinib was designed to block the activation loops of KIT and PDGFRα, at sub-nanomolar potency in GISTs with *PDGFRA* D842V and KIT D816V mutations. It also blocks the ATP/imatinib binding site in GISTs with mutations in exon 17 and exon 18. A Phase I study that included a heavily pretreated population showed impressive activity in PDGFRA D842V mutant GIST. Grade 3–4 toxicities were observed in 25% of patients (17,18). Based on these striking results, a Phase III trial of Blu-285 is being tested in the third-line setting of metastatic GIST. Other clinical trials include combinations of KIT and

MEK (mitogen-activated protein kinase enzymes MEK1 and/or MEK2) inhibitors to cause destabilization of ETV1 (ETS variant 1) resulting in downregulation of KIT (19). Pexidartinib is another strong KIT inhibitor, with preferential activity against tumors with mutations in exon 13/14 (20).

Next generation sequencing (NGS) has revolutionized genomic research and clinical oncology testing. NGS performs sequencing of millions of small fragments of DNA in parallel in a short period of time compared to Sanger's sequencing technology. NGS provides unique information that may drive meaningful decisions in the treatment of rare tumors such as GIST. In addition to information regarding mutations in *KIT* and *PDGFRA*, NGS may be used to simultaneously test for targets in which potent drugs are available or under development targeting *KRAS*, *BRAF*, *MSI*, *HER2*/neu, and potent fusion genes such as *FGFR* and *NTRK* agnostic of tumor sites (21,22). For instance, the tropomyosin receptor kinase (TRK) receptor family comprises 3 transmembrane proteins receptors, TRKA, TRKB and TRKC that are encoded by the *NTRK1*, *NTRK2* and *NTRK3* genes, respectively. The frequency of mutations in this gene family is highly variable (>90% in infantile fibrosarcoma, ~10% in high-grade pediatric gliomas, to ~1% in adult sarcomas). In common cancers like NSCLC, *TRK* fusions tend to be a rare event, occurring in only 0.5% to 1%. And there are many rare cancers where *TRK* fusions are defining molecular aberration. These fusion genes may be found in *KIT/PDGFA/BRAF* mutation negative GISTs. Larotrectinib is a selective pan-TRK inhibitor that in a clinical trial of adult and pediatric patients whose tumors harbor *NTRK* gene fusions, the overall response rate was reported to be 76% (12). Additionally, the majority of the patients continue to benefit from the drug without progression. The drug received FDA approval in November 2018 for the treatment of solid tumors (in adult and pediatric patients) that have an NTRK gene fusion; are metastatic or where surgical resection is likely to result in severe morbidity; and have no satisfactory alternative treatments or that have progressed following treatment.

Other drug discovery approaches have identified repurposed drug with potential clinical utility. For example, Pessetto and colleagues reported through a quantitative drug screen of FDA-approved drugs in GIST cells that four drugs, auranofin, bortezomib, idarubicin HCl, and F-AMP, demonstrated selective anticancer activity as single agents (23). In our subsequent study, we demonstrated the combination of imatinib and F-AMP substantially enhanced the antitumor effects compared to imatinib alone. These studies suggest that repurposed drug screens may be useful to identify unappreciated drugs with the potential to work in combination with imatinib for the treatment of both primary and imatinib-refractory tumors (23,24).

At the University of Kansas Institute for Precision Medicine, tumors from patients with GIST are routinely sent for NGS gene panel testing to the Clinical Molecular Oncology Laboratory (CMOL). The CMOL is a CLIA approved and CAP accredited laboratory that provides rapid and high-quality molecular cancer diagnostic testing for patients, which is an essential component of personalized care. Our gene panels include testing for mutations in *KIT* and *PDGFRA*, *SDHA*, *B*, *C*, *D*, *BRAF*, *KRAS*, and mutations in potent fusion genes like *NTRK*. With the advent of cancer immuno-based therapies (25) we are now providing tumor mutation burden (TMB) scores and microsatellite instability (MSI) status using larger NGS gene panels. Some of these patients will have blood draws for cell-free DNA (cfDNA) as well. The results are discussed in the multidisciplinary Molecular Tumor Board for sound interpretation of these NGS results and their subsequent translation to personalized care of the patients in the clinic.

The universal use of NGS for large gene panels, whole exomes or genomes may be cost-prohibitive and impractical if done for tumors such as GISTs with clear oncogenic mutations. The identification of patients harboring rare but very potent oncogenes translate to significant improvement in outcome with use of drugs targeting these mutations. It is time to take the guesswork and blind-folded approach out of our way of treating this rare but treatable disease. We continue to endorse NGS testing using a comprehensive but GIST-focused gene panel to include not only testing for mutations in the coding sequences of *KIT* and *PDGFRA* but also additional molecular targets for which drugs are available or are in development that will move the survival of these patients to levels that will get them across the valley of death. Based on these and other advancements defining the molecular landscape of the cancer, GIST may be one of the first solid tumors to be completely controlled in our lifetime, thus delivering on the promises of precision medicine.

Acknowledgments

Funding: This report was supported in part by The Kansas Institute for Precision Medicine (1P20GM130423 to A.K.G.). A.K.G. is the Chancellors Distinguished Chair in Biomedical Sciences.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gastrointestinal Stromal Tumor*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gist.2019.10.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/gist.2019.10.01
Cite this article as: Baranda JC, Godwin AK. Advancing the promises of precision medicine for patients with gastrointestinal stromal tumor. Gastrointest Stromal Tumor 2019;2:4.

