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Review Article

Consensus or Controversy --- Should Mutational Analysis (MA) be Considered as a "Routine Testing" in the Clinical Management of Gastrointestinal Stromal Tumor (GIST) in the Era of Personalized Medicine?

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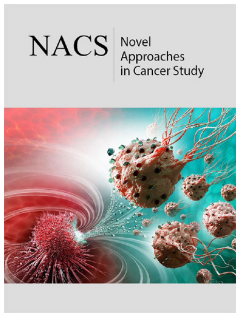

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Abstract

Unique amongst most solid malignancies, gastrointestinal stromal tumors (GISTs) are addicted to a few specific oncogenic drivers and are uniformly resistant to cytotoxic chemotherapeutics but sensitive to tyrosine kinase inhibitors (TKIs). Similar to all cancers, GISTs are heterogenous and subclassified into distinct entities according molecular alterations. It is unquestionable that mutational status offers both prognostic as well as predictive value to guide clinical management of GISTs in both advanced/metastatic and curative/(neo)adjuvant settings. One would therefore assume that mutational analysis would be routine and adopted routinely in terms of timing in the clinical management of GIST, but in practice the assessment of mutational analysis is not adopted routinely. In this paper we will discuss the impact of mutational analysis on clinical management of GIST, as well as review currently guidelines for mutational analysis and review possible reasons for lack of uptake of routine testing in practice.

Prevalence and Type of Molecular Mutations in GISTs

As with other malignancies, GISTs evolve over time and may develop various types of mutations over the disease trajectory. At diagnosis, it is known that most GISTs, in fact roughly 70-90% of GISTs contain various types of gain of function mutations in KIT (exons 9 (~10%), 11 (~70%), 13(~2%), 17(~1%)) or platelet derived growth factor alpha (PDGFR**α**) (exons 12 (~1%), 14 (~1%), 18 (~8%)) oncogenes [1]. ~10-15% of GISTs are so called wild-type (wt) GISTs that do not contain KIT/ PDGFR**α** mutations [1]. About 20-40% of wt GISTs overexpress insulin growth factor 1 receptor (IGF1R) and have loss of expression of the succinate dehydrogenase complex either due to mutations in one of four SDH subunits (SDHA/SDHB/SDHC/SDHD) or promoter hypermethylation of SDHC collectively defined as SDH-deficient GISTs [2]. The rest of wt GISTs may contain alterations affecting the gene for neurofibromatosis 1 (NF1) or genes coding for members of the RAS signaling pathway such as BRAF (~4%)/RAS (<1%)/PIK3CA (<1%) [3]. GISTs that do not contain mutations in KIT/PDGFR**α**/RAS pathway/SDH mutations are referred as quadruple wt GISTs, likely in the range of ~5% in prevalence [4]. ETV6-NTRK3 and FGFR1-TACC1 translocation are recently identified in quadruple wt GISTs [5-7].

The Impact of Mutation Analysis on Management of Advanced/Metastatic GISTs

In 2002, shortly after a breakthrough case report immediately followed by a single open-label clinical study (randomized to different doses) [8,9], the FDA granted accelerated approval of the first molecularly targeted agent imatinib in unresectable/metastatic GISTs. Since then, the median overall survival of advanced GISTs has drastically improved from less than 1 year to about 5 years with over 20% long-term survivors (≥10 years) [10]. This agent therefore became the standard of care for first line treatment of metastatic/unresectable GIST. In the face of progressive disease, it was found that increasing the dose of imatinib was

effective [11], and subsequently further studies assessed the role of alternate TKIs beyond progression. Sunitinib [12] and regorafenib [13] are approved standard second- and third-line treatments which can potentially further extend overall survival for patients with advanced GISTs who failed first line imatinib. After failing all 3 standard lines of treatment, rechallenge with imatinib may provide a small benefit with short duration [14]. Other tyrosine kinase inhibitors (sorafenib [15,16], nilotinib [17], panzopanib [18,19] and others reviewed in [20]) may have some activity beyond second line settings. Clinical trials are considered for patients who continue to have good performance status after failing standard treatments as described. Very recently, a few promising targeted drugs such as aprotinin (Blu285) [21,22] and Ripretinib (DCC-2618) [23] which are currently actively investigated in the clinical trials (Clinicaltrials.org NCT03353753, NCT03673501, NCT03465722), have demonstrated significant activity in previously heavily treated GIST patients with a RR of ~20% (third line beyond), reported by George et al and Heinrich et al at the CTOS meeting 2018 [24,25]. Despite what appears a simplified and straightforward sequential therapeutic strategy (imatinib 400mg/day → imatinib 800mg/day → sunitinib → regorafenib → recycle imatinib or clinical trials in patients who maintain good performance status) in managing advanced/metastatic GISTs, it is indisputable that mutational analysis provides significant prognostic and predictive information, which can potentially alter the standard sequence of treatment options and optimize personalized treatments.

Metastatic GISTs with KIT exon 11 mutations have superior response rate (RR) to imatinib of over 80-90% that is durable with a median progression free survival (mPFS) of over 3 years and 69% patients with these tumors still alive at 5 years 26. Furthermore, this particular mutation strongly predicts long-term survival (≥10 years) [26]. It is noticeable that different types of KIT exon 11 mutations may have different imatinib sensitivity and prognosis1. After progression on imatinib, these tumors derive the least benefit from sunitinib than GISTs with exon 9 mutations and wt GISTs [27]. Metastatic GIST patients with tumors bearing KIT exon 9 mutations treated with imatinib 800mg/day have significantly higher RR and longer mPFS than those who were treated with imatinib at 400mg/day [28-30], suggesting KIT exon 9 mutated GIST tumors are imatinib dose-dependent and patients with these tumors should be treated at higher dose of imatinib with 800mg/day upfront. In addition, these tumors appear more sensitive to sunitinib compared to GISTs with KIT exon 11 mutations after failing imatinib [27]. Many GISTs with PDGFR**α** mutations are variably sensitive to TKIs with the exception of GIST with exon 18 p. D842V that are notoriously resistant to all TKIs, but responded remarkably to avapratinib (Blu285) with 84% objective response rate (ORR) and 9% complete response (CR) in the setting of previously heavily treated advanced stage [21,22,25]. On the other hand, GISTs with PDGFR**α** p.V654A and p.T670I mutations were associated with significantly lower RR [25]. Therefore, metastatic patients with PDGFR**α** p.D842V mutated GISTs should not be treated with standard TKIs which could potentially lead to unnecessary toxicities and delay effective treatment/clinical trial opportunity. Only a subset of wt GISTs is sensitive to imatinib, many are not, in particular GISTs with NF1 mutations [31]. These tumors may be sensitive to MEK inhibitors [32]. SDH- deficient GISTs may be more sensitive to sunitinib [18] or regorafenib [33] compared to imatinib. IGF1R inhibitors may be another novel therapeutic option [34]. GISTs with rare ETV6-NTRK3 fusion may respond extraordinarily to NTRK inhibitors [7]. BRAF inhibitor is an attractive targeted option for GISTs with BRAFV600E mutation [35] despite the fact that these tumors do not have BRAF protein overexpression or MAPK pathway activation compared to tumors without BRAF p.V600E mutation. Similar as above, patients with metastatic GIST harboring these specific genetic alterations should be encouraged to participate in clinical trials with the possibility of receiving novel targeted therapy as opposed to standard sequential TKIs.

The Impact of Mutation Analysis on Management of Resectable GISTs

For resectable GISTs, tumor characteristics including size, location, mitotic count and perforation as well as patients' characteristics including comorbidities and functional status are considered standard factors to decide if a patient is suitable for neo(adjuvant) imatinib, though tumor anatomic location and surgeon's preference take precedence in the neoajuvant setting. Imatinib 400mg/day for approximately ~6-9 months till maximum response achieved before surgery for patients diagnosed with locally advanced GISTs sespecially in anatomically "challenging" locations (gastroesophageal junction, duodenum and rectum) and continued after surgery for a total duration of 3 years [36,37] or imatinib 400mg/day for 3 years for patients diagnosed with resected high risk GISTs remain as standard of care [38]. However, several important questions remain to be addressed including optimal duration and dosing of imatinib in the (neo)adjuvant setting. In addition, the benefit of adjuvant imatinib for GIST patients with intermediate risk remains unclear [39]. It is notable that clinicians tend to underestimate the risk in patients with GIST tumors of intermediate size, intermediate level of mitotic count, and non-gastric locations which may negatively impact on clinical decision for adjuvant therapy [40]. Upfront mutational analysis may help to further risk stratify patients with resectable GISTs to guide and optimize personalized adjuvant treatments.

GISTs with KIT exon 11 deletion mutations portend a high risk of recurrence [41] after curative surgery but benefit the most from adjuvant imatinib especially with longer duration, compared to other types of KIT mutations as well as other genetic alterations [42,43], likely due to the exquisite sensitivity to imatinib that are consistently observed in metastatic setting [26]. Two recent retrospective studies showed that intermediate GISTs with exon 11 deletion mutations are associated with an inferior clinical outcome with relapse free survival (RFS) similar to high-risk GISTs [44] but may have better clinical outcome with adjuvant imatinib than placebo [45]. All these data support the need for future prospective clinical trials to specifically evaluate the benefit of adjuvant imatinib and its optimal duration in intermediate GIST tumors with exon 11 deletion mutations. While eagerly awaiting SSG XXII study (Clinical

Trials.gov identifier: NCT02413736) evaluating the benefit of 5 years (versus 3 years) of imatinib in high risk GISTs, it is tempting to hypothesize that longer duration of adjuvant imatinib (>3 years) may be beneficial for high risk GISTs with exon 11 deletion mutations which may resemble the clinical scenario of adjuvant endocrine treatment for hormone receptor positive breast cancers [46]. GISTs with KIT exon 9 mutations also has a relative high risk of recurrence after curative surgery41 but benefit less to imatinib at standard dose of 400mg/day compared to GISTs with KIT exon 11 mutations [42,43]. One of the few patients (7/91) who recurred on planned 5 years of imatinib at 400mg/day in the PERSIST-5 clinical trial had KIT exon 9 mutation [47], suggesting that higher dose (800mg/day) of adjuvant imatinib may be needed for these tumors. This was recommended in recent guideline [48]. While PDGFR**α** mutations are rare (~1-3%) in advanced GISTs, they are much more prevalent in early stage GISTs (10-20%) with the majority (>90%) occurring in patients with tumour in the prognostically favorable gastric location, suggesting an indolent behavior of many of these tumors [41], which may not benefit adjuvant imatinib [43]. PDGFR**α** p.D842V is one of the most common (60-65%) PDGFR**α** mutations that is known to resistant to imatinib and other TKIs. In the PERSIST-5 clinical trial, 2 patients (out of 7) recurred and one of them died on planned 5 years of imatinib at 400mg/day had PDGFR**α** D842V mutations [47], suggesting these tumors should not be treated with adjuvant imatinib. Wt GISTs generally have relative better prognosis after curative surgery [41] and many of these tumors especially NF1 mutated ones are not sensitive to imatinib, consistent with the clinical finding of no potential benefit of adjuvant imatinib in these tumors [43,47]. Further clinical trials are warranted to define a subset of wt GISTs that could potential derive benefit from adjuvant therapy.

Underuse of Mutational Analysis-Discordant with Recent Clinical Guidelines' Recommendations

The National Comprehensive Cancer Network (NCCN) [49], European Society of Medical Oncology (ESMO) [48] and UK guidelines [50] consistently recommend upfront mutational analysis at the time of diagnosis of GIST with the possible exclusion of < 2cm non-rectal GISTs as they rarely require any systemic treatments [48]. In addition to this, a survey study revealed that >90% of physicians agree that mutational analysis is a valuable tool that help guide treatment decision in both (neo) adjuvant and metastatic setting [51]. Despite this intent and despite the international guidelines, there is still significant underuse (15-40%) of mutational analysis in GIST clinical management, more so in the (neo)adjuvant than metastatic setting, has been reported in the studies conducted both in US and Europe [51-53]. However, some of these studies were done preceding the date of recently published guidelines. It would be interesting to compare if there is any practice pattern change before and after these guidelines were published. This study is currently planned in our institution. The limited availability of the test (varied among different institutions and countries) which could be related to lack of quality assurance program, laboratory infrastructure, or other logistic reasons and cost burden associated with reimbursement issues may explain the low uptake of routine mutational analysis. However, it is puzzling that in developed countries with advanced healthcare systems where mutational analysis is readily available without much logistic hurdles, routine use of mutational analysis is limited, as in the case of the US [51]. Further study is needed to identify the barriers faced by practicing GIST/sarcoma oncologists in countries where mutational analysis is readily available and cost/reimbursement issue is of no concern. Indeed, ongoing survey studies are being conducted at several centers internationally, including BC Cancer Agency amongst others. Historically, only focused KIT and/or PDGFR**α** genotyping (by Sanger sequencing) was available in most high-volume GIST/sarcoma reference center. The cost of KIT/PDGFR**α** genotype is variable among geographic regions but mostly ~$750 or under. With gradual clinical deployment of next generation sequencing (NGS) in recent years, test performance, quality and, turn- around-time are significantly improved even with limited sample material that has suboptimal tumor cell content compared to conventional methods. The introduction of whole genome or exome NGS in the routine diagnostic setting is still debatable due to the complexity of the assay and prohibitive cost (~$5000-10,000) [54]. However, targeted NGS panel testing platform offers an attractive alternative to perform multiplex detection of essential genetic alterations (KIT/PDGFR**α**/SDHB/BRAF/RAS/NF1 etc.,) to improve tissue efficiency, provide actionable information, and as well may be more cost efficient. This panel-testing platform has been introduced into the clinic practice for most academic centers in the last few years with a cost of approximately of less than $2000 per test. Additionally, newer NGS panels cover prognostically- and therapeutically- critical DNA and RNA alterations the latter include potentially targetable fusion events such as those involving NTRK1-3. Considering the cost of TKIs which range between $2000 to over $7000 per month, the duration of adjuvant imatinib, and the prevalence of potential treatment-resistant GISTs, routine mutational analysis may be cost-effective hypothetically, however, this needs to be further evaluated by a thorough analysis of molecular epidemiology of GISTs in the context of various risk stratification [55]. In the era of personalized medicine, where GIST is one of leading exemplary paradigm shift with unprecedented improvement with targeted therapies, it would be imperative to explore if routine mutational analysis would further improve the clinical outcome of GIST patients in a cost-effective manner. In addition, the barriers to adopting this strategy in routine practice will need to be clearly identified and pragmatically addressed.

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