PHASE I RESULTS FROM A MULTI-PHASE COMPREHENSIVE GENOMIC SEQUENCING TUMOR STUDY IN GASTROINTESTINAL STROMAL TUMOR PATIENTS

Denisse Montoya, Sahibjeet Kaur, Antoinette Pauwels, Olivia Regan, Katie Regan, Jerry Call, Jim Hughes, Sara Rothschild.

The Life Raft Group, Wayne, NJ

INTRODUCTION

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Most GISTs harbor a mutation located in either KIT or platelet-derived growth factor receptor alpha (PDGFRA). Over the last few decades, advances in GIST have led to the approval of multiple targeted therapies. Imatinib, one of the frequently used therapies for GIST, has demonstrated low sensitivity among KIT/PDGFRA wildtype GISTs. Comprehensive genomic profiling (CGP) is used to optimize the therapy selection due to its ability to detect underreported pathogenic biomarkers and allowing a more tailored approach to therapy in both primary and metastatic settings

ABSTRACT

Objective

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Most GISTs harbor a mutation located in either KIT or platelet-derived growth factor receptor alpha (PDGFRA). Over the last few decades, advances in GIST have led to the approval of multiple targeted therapies. Imatinib, one of the frequently used therapies for GIST, has demonstrated low sensitivity among KIT/PDGFRA wildtype GISTs. Comprehensive genomic profiling (CGP) is used to optimize the therapy selection due to its ability to detect underreported pathogenic biomarkers and allowing a more tailored approach to therapy in both primary and metastatic settings. Several targetable drivers including neurotrophic tyrosine receptor kinase (NTRK) fusions have been identified by using CGP and could benefit patients with FDA approved therapies. Despite the advances of therapies and the known importance of CGP, the rate of CGP is relatively low in patients with GIST. The present study reports results from Phase I of our multi-phase study, which will demonstrate the various genomic drivers that exist in this population and the potential impact of treatment trajectory for patients.

Methods

Next generation sequencing (NGS) based biomarker analysis was performed on tumor DNA and RNA focusing on wildtype GIST subgroups and included NTRK gene fusion. Patient recruitment involved The Life Raft Group (LRG) GIST Patient Registry members, direct patient outreach via phone and email, social media, and physician referral with a proposed sample size of 255 patients to be tested at the end of the multiphase study. Eligible patients were required to reside in the USA, have never received any form of genomic testing for their GIST diagnosis, be an active member of the LRG GIST Patient Registry, and have viable formalin-fixed, paraffin-embedded (FFPE) tissue slides or blocks available for testing. Patients who showed a wildtype KIT/PDGFRA result from a previous basic KIT/PDGFRA mutational test were also eligible. The test featured a 20 gene panel including sequencing coding DNA of all the exons within the genes plus an additional 50 nucleotides at the 5' and 3' ends of each coding exon to detect splicing abnormalities. Reports were shared with the patient and treating physician to aid in treatment selection. Results from Phase I were analyzed to understand the impact within the patient cohort and potential therapy changes.

Results

104 patients expressed interest in the study. 55 (53%) patients were qualified for testing while 49 (47%) patients were not qualified. Out of the 49 unqualified, 18 (37%) did not meet residency requirements, 19 (39%) did not have any tissue available for testing and 12 (24%) patients already had CGP performed but were unaware or had not reported results to the patient registry. Tumor tissue from 55 eligible patients was processed through NGS. Patient characteristics from this cohort are portrayed in Table.1. Out of the samples tested, 32 (58%) patients had a previous wildtype KIT/PDGFRA reported mutation and 23 (42%) patients never had received CGP. 29 (53%) patients received a Test Not Performed (TNP), Quantity Not Sufficient (QNS) or showed results with Variants of Unknown Significance (VUS). Biomarkers were identified in 26 (47%) patients. Remarkably, NTRK ETV6-fusion positive was present in 2 (2/26; 8%). Half of the mutations detected were KIT mutations (13/26; 50%). PDGFRA mutation was present in 2 (8%) patients, VUS in EGFRA mutation was detected in one patient. 3 (11%) patients showed an NF1 mutation, with a dual mutation of SDHB and NF1 detected in one patient. SDHA mutation was present in 6 (23%) patients (See Figure.1). With these results, 11 (42%) patients had to change or adjust their medication to ensure the most effective treatment plan.

Conclusion

Utilizing NGS based CGP is a crucial step in understanding and identifying relevant biomarkers including tumor growth drivers to aid in the treatment decision for optimal patient outcomes. CGP provides relevant data for conducting a more accurate, individualized treatment plan for patients, and prevents patients from undergoing unnecessary therapies that will not work for their respective mutation. Furthermore, this approach accelerates adoption of precision oncology and aids future drug discovery and development programs specifically for GIST patients. Genomic characterization is a critical point in the treatment course of countless GIST patients and should be considered the standard practice for GIST patients that qualify for oral chemotherapy treatment. Based on Phase I findings, a Phase II study is underway to explore additional genomic drivers that may exist in this population, and how targeted therapies can change the treatment trajectory and outcome for patients. Phase II will expand CGP to feature a 648 gene DNA panel sequence, Microsatellite Instability (MSI) status, Tumor Mutational Burden (TMB), and full transcriptome analysis by RNA sequencing. Patient-matched germline DNA will also be explored to further understand the genomic landscape in GIST.

OBJECTIVE

To present study reports results from Phase I of our multi-phase study, which will demonstrate the various genomic drivers that exist in this population and the potential impact of treatment trajectory for patients.

METHODS

CGP was performed on tumor DNA and RNA focusing on wildtype GIST subgroups and included NTRK gene fusion. The test featured a 20 gene panel including sequencing coding DNA of all the exons within the genes plus an additional 50 nucleotides at the 5' and 3' ends of each coding exon to detect splicing abnormalities

RESULTS

- 104 patients expressed interest in the study. 55 (53%) patients were qualified for testing while 49 (47%) patients were not qualified.
- Out of the 49 unqualified, 18 (37%) did not meet residency requirements, 19 (39%) did not have any tissue available for testing and 12 (24%) patients already had CGP performed but were unaware or had not reported results to the patient registry. Tumor tissue from 55 eligible patients was processed through NGS.

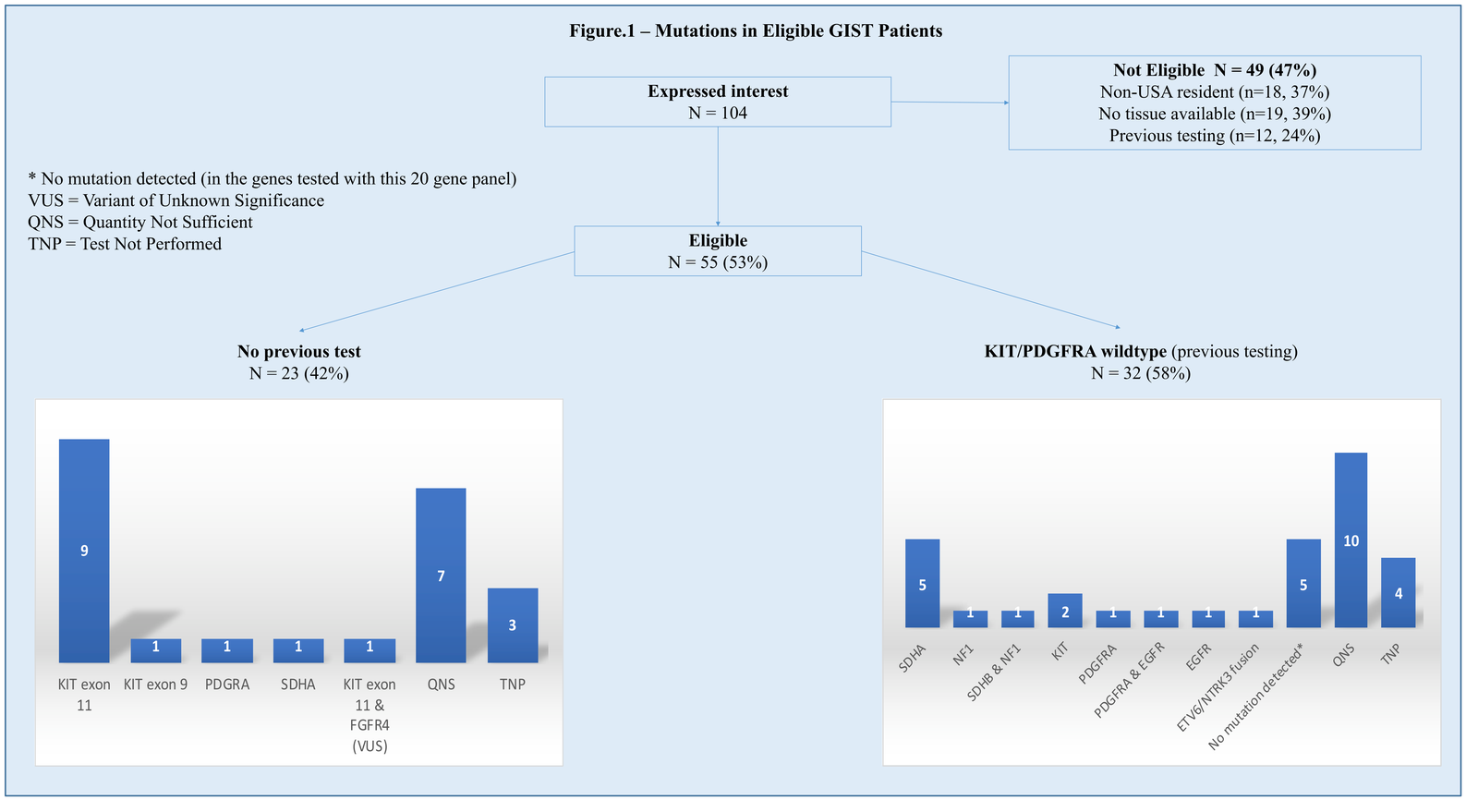
Table.1 Summary of patient cohort from Phase I

Gender	N (%)	Ethnicity	N (%)	Year of Specimen Collection	N (%)
Female	39 (71%)	White, not of Hispanic origin	37 (67%)	<2005	8 (15%)
Male	16 (29%)	American Indian	1 (2%)	2006-2010	7 (13%)
		Asian or Pacific Islander	4 (7%)	2011-2015	8 (15%)
Stage at Diagnosis	**N (%)**	Black, not of Hispanic origin	5 (9%)	2016-2020	26 (47%)
Single tumor at diagnosis	47 (85%)	Hispanic	7 (13%)	2021	6 (11%)
Metastatic at diagnosis	6 (11%)	Unknown/Not Reported	1 (2%)		
Multi-focal at diagnosis	2 (4%)				
Primary Tumor Location *	**N (%)**	**Risk of Recurrence**	**N (%)**	**Year of Diagnosis**	**N (%)**
Rectum	1 (2%)	High Risk	34 (62%)	<2005	8 (15%)
Small Intestine	14 (29%)	Intermediate Risk	6 (11%)	2006-2010	12 (22%)
Stomach	29 (59%)	Low Risk	10 (18%)	2011-2015	7 (13%)
Unknown	5 (10%)	Unknown	5 (9%)	2016-2020	23 (41%)
				2021	5 (9%)

*Primary tumor location for non-metastatic patients only

- Out of the samples tested, 32 (58%) patients had a previous mutation test reporting KIT/PDGFRA wildtype, and 23 (42%) patients never had received CGP.
- 29 (53%) patients received a Test Not Performed (TNP), Quantity Not Sufficient (QNS) or showed results with Variants of Unknown Significance (VUS).
- Biomarkers were identified in 26 (47%) patients. Remarkably, NTRK ETV6-fusion positive was present in 2 (2/26; 8%). Half of the mutations detected were KIT mutations (13/26; 50%). PDGFRA mutation was present in 2 (8%) patients, VUS in EGFRA mutation was detected in one patient. 3 (11%) patients showed an NF1 mutation, with a dual mutation of SDHB and NF1 detected in one patient. SDHA mutation was present in 6 (23%) patients.
- With these results, 11 (42%) patients had to change or adjust their medication to ensure the most effective treatment plan.

Figure.1 – Mutations in Eligible GIST Patients



CONCLUSIONS

- The vast majority of wildtype *KIT* and *PDGFRA* tumors detected by basic mutational testing can and should be further classified.
- CGP found KIT (2) and PDGFRA (2) mutations in patients previously identified as KIT/PDGFRA Wildtype.
- CGP provides relevant data for a more accurate, individualized treatment plan for patients, and prevents patients from undergoing unnecessary therapies that will not work for their respective mutation.
- Phase II study is underway to explore additional genomic drivers and how targeted therapies can change the treatment trajectory and outcome for patients.
- Phase II will expand CGP to feature a 648 gene DNA panel sequence, Microsatellite Instability (MSI) status, Tumor Mutational Burden (TMB), and full transcriptome analysis by RNA sequencing. Patient-matched germline DNA will also be explored to further understand the genomic landscape in GIST.

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