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Clinical practice and outcomes in advanced gastrointestinal stromal tumor: Experience from an Indian tertiary care center

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Abstract

Background: Management of advanced Gastrointestinal stromal tumors (GIST) has been revolutionized with the use of Imatinib guided by mutation analysis. Data from India remains scarce. **Materials and Methods:** Patients with metastatic GIST who were treated at Department of Gastro-intestinal & Hepaticopancreaticobiliary Oncology Unit at Tata Memorial Hospital, Mumbai between December, 2004 and December 2015 were included in the analysis. Clinical and radiological data was retrieved from stored medical records and charts. **Results:** A total of 83 patients with metastatic GIST were available for analysis. Median age was 54 years with a 3:1 male predominance. Stomach was the most common site of primary with liver being the most common site of metastasis. c-Kit mutation analysis results were available for 44 patients with exon 11 mutant being the most common mutation. With a median follow up of 33 months, the 10 years estimated progression free and overall survival (OS) was 18% and 51% respectively. Overall response rate to first line imatinib was 37.6% and estimated 3 years OS to first line therapy was significantly better for Exon 11 mutated patients (p=0.016). 34 patients received second line therapy in the form of either sunitinib, pazopanib or increased dose imatinib with a clinical benefit rate of 73.5%. C-Kit mutated patients had a better median OS compared to non mutated patients. **Conclusions:** GIST diagnosed and treated in the Indian subcontinent appears to show improved outcomes. The importance of c-Kit mutation analysis in determining the prognosis and outcomes of patients with advanced GIST is emphasized.

Key words: Imatinib, KIT mutation analysis, metastatic gastrointestinal stromal tumor

Introduction

Currently, the median survival of patients with advanced gastrointestinal stromal tumor (GIST) approximates 55 months in certain studies, with differences seen in the performances of patients with exon 11 versus exon 9 c-KIT mutation status.[1] This extended survival is due to the performance of first-line imatinib as well as being able to expose a patient to further lines of therapy with approved options such as sunitinib, pazopanib, and regorafenib.[2-6] This may not always be feasible in a financially constrained real-world population, like India, where cost and access to expensive targeted therapies may be limited.

With this background, this study was conducted to evaluate the characteristics and outcomes of patients with advanced GIST treated at our institution, with a focus on the performance of imatinib as well as further treatment strategies postprogression on imatinib.

Materials and Methods

The prospectively maintained GIST database at the Department of Gastrointestinal and Hepatopancreaticobiliary Oncology Unit at Tata Memorial Hospital, Mumbai, between December 2004 and December 2015, was examined, and patients with metastatic GIST had their details extracted for analysis. Baseline demographic, clinical, and radiological data was retrieved along with c-KIT mutation analysis which was performed using reverse transcriptase polymerase chain reaction (PCR) technique. Response to treatment was recorded clinically and radiologically using RECIST version 1.1 criteria[7] at 2–3-month intervals.

Testing for c-KIT mutations

Archived formalin-fixed, paraffin-embedded (FFPE) tissues of histologically and immunohistochemically proven GIST tumor samples were used for testing KIT exons 9, 11, 13, and 17 by PCR. Purified PCR products were subjected to direct DNA sequencing in both directions using BigDye version 3.1 cycle sequencing kit (Applied Biosystems, USA). Sequences were analyzed using sequence analysis software SeqScape® (Applied Biosystems) and Chromas Lite (Technelysium Pvt. Ltd) and were compared with the wild-type KIT reference sequence, with the mutations being reported as per the recommendations of the Human Genome Variation Society. The reference sequence used in this study is KIT (gene ID 3815). The Single Nucleotide Polymorphism database (dbSNP), Catalogue of Somatic Mutations in Cancer (COSMIC), and ensembl databases were referred before considering the abnormal results as "novel mutations." Samples which were nonamplified, with noise or with nonreadable sequences, were repeated once before considering them as uninterpretable.

Statistics

Demographic characteristics have been presented as descriptive statistics in percentages. Progression-free survival (PFS) was calculated from the date of start of treatment to the date of clinical or radiological evidence of disease progression or the last follow-up date. Overall survival (OS) was calculated from the date of start of treatment until last follow-up or death. Survival analysis was performed using Kaplan–Meier estimates and log-rank test for bivariate comparisons. c-KIT genotype relationship with outcome was assessed for patients whose genotypic information was available. Multivariate analysis was performed using Cox proportional hazard analysis. Data were censored for analysis on December 31, 2015. SPSS Statistics (IBM) version 20 was used for statistical analysis.

Results

Eighty-three patients of metastatic GIST were treated with first-line imatinib at our center between December 2004 and

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December 2015. Median age at diagnosis was 54 years (range 21–76). Male:female ratio was 3:1. Primary sites of disease were stomach 32 (38.6%), small intestine 27 (32.5%), duodenum 2 (2.4%), anorectal 4 (4.8%), retroperitoneal 6 (7.2%), colon 2 (2.4%), ovarian 3 (3.6%), gallbladder 1 (1.2%), and unknown 6 (7.2%).

Sites of metastasis were liver 68 (81.9%), peritoneum 27 (32.5%), lung 2 (2.4%), bone 2 (2.4%), nodal 7 (8.4%), ovarian 1 (1.2%), and pancreatic 1 (1.2%).

Prior adjuvant therapy was received by 21 patients (25.3%) and the median duration of adjuvant therapy was 24 months (range: 4 - 60 months). Mutation status was wild type 8 (9.6), single exon mutation 28 (33.7), complex mutation 8 (9.6), and not available in 39 (47) patients, respectively. c-KIT mutation profile was exon 11 in 29 (34.9), exon 9 in 5,[6] exon 13 in 5 (6), and exon 17 in 3 (3.6) patients.

Response to first-line imatinib

All the 83 patients with metastatic GIST were started on first-line imatinib during the specified time period. Median duration on imatinib in first line was 34.3 months. Five patients (6%) had a complete response (CR), 26 (31.3%) had partial response, 40 (48.2%) had stable disease (clinical benefit rate: 85.5%), and 8 (9.6%) had progressive disease as best response. Response assessment was not available in 4 patients (4.8%).

Progression on first-line imatinib was seen in 37 patients (44.6%), and imatinib was discontinued in three patients due to toxicity. Of these forty patients, six patients were offered best supportive care postprogression on imatinib owing to their poor performance status. Thirty-four patients received second line with either an increased dose of imatinib, sunitinib, or pazopanib.

Thirty-three patients still continue to be on first-line imatinib as of now while ten patients are lost to follow-up while on first-line imatinib. The response rates to first-line imatinib were not significantly different with respect to the mutation status.

The median follow-up duration was 33 months. The estimated 10-year OS was 51%. The OS was significantly longer for patients with exon 11 mutation than those with exon 9 mutation or wild-type c-KIT (3-year OS – exon 11 vs. exon 9 vs. wild – 93.3% vs. 80% vs. 52.5%; $P = 0.016$).

The median PFS on first-line imatinib was 39 months with a 10-year PFS of 18%. The PFS was significantly better for patients with exon 11 mutation as compared to exon 9 mutation or wild-type c-KIT (median PFS – exon 11 vs. exon 9 vs. wild type – 37 months vs. 15 months vs. 11 months; $P = 0.035$).

Second-line treatment

Thirty-four patients received second-line treatment. Sunitinib was started as second-line treatment in 19 patients (55.9%) while imatinib dose was escalated in ten patients (29.4%). Pazopanib was started as a second-line treatment in five patients (14.7%). Two patients (5.9%) had CR, 3 (8.8%) had partial response, 20 (58.8%) had stable disease (clinical benefit rate: 73.5%), and 8 (23.5%) patients had progressive disease as best response. Response evaluation details were not available for one patient (2.9%). Twenty patients (58.8%) progressed on second-line treatment while it was discontinued in one patient due to toxicity. Thirteen (38.2%) patients continued to be on second-line treatment at the time of censoring. Third-line treatment was offered in 16 patients (47.1%) whereas five patients (14.7%) were considered for best supportive care.

Median PFS for second-line treatment was 13 months with a 3-year PFS of 8%. Sunitinib in second line tended to have a better median PFS as compared to other second-line treatments, but it was not statistically significant (sunitinib vs. dose-escalated imatinib or pazopanib – 15 months vs. 10 months; $P = 0.09$). The median PFS for second-line treatment for patients with exon 11 mutation was 29 months as compared to 8 months with exon 9 and 6 months with wild type ($P < 0.05$). The median PFS in second line for patients with any c-KIT mutation was 22 months as compared to 6 months in c-KIT wild type ($P < 0.05$).

The 3-year OS for second-line treatment was 59% with a median OS of 36 months. There was no OS difference for patients with respect to the second-line agent received. The 2-year OS in second line for patients with any c-KIT mutation was 56% as compared to 38% in c-KIT wild type ($P < 0.016$). Further study of correlation of survival with respect to exon 11 or exon 9 was not feasible in view of small population.

Third-line treatment

Sixteen patients received third-line treatment, of which nine patients (56.3%) received pazopanib, imatinib rechallenge in three patients (18.8%), sorafenib in two patients (12.5%), and one patient (6.3%) each received sunitinib and regorafenib. None of these patients attained CR while one patient had a partial response and stable disease was seen in four patients. Nine patients (56.3%) eventually progressed on third-line treatment while two patients (12.5%) discontinued due to toxicity. Five patients (31.3%) were still on third-line treatment at the time of data censoring. The median OS and PFS with third-line treatment were 12.2 and 8 months, respectively.

Discussion

The median PFS of 39 months with first-line imatinib and a 10-year PFS and OS of 18% and 51% in our study, respectively, was significantly better than what has been reported in one of the landmark trials with the longest follow-up to date.[1]

PFS and OS times did not differ significantly according to c-KIT mutation status which is similar to other studies from the Asian subcontinent.[8] Kim *et al*. analyzed the relationship between treatment outcome and kinase mutational status in 113 Korean patients with advanced GISTs treated with imatinib.[9] However, in our study, exon 11 mutant isoforms were associated with a longer PFS and OS as compared to exon 9 mutants or wild type in univariate analysis. This is consistent to that reported by Heinrich *et al*.[10]

Data from the Indian subcontinent regarding the impact of mutational status beyond first-line imatinib are lacking. The median PFS with second-line treatment was 12 months while with second-line sunitinib was 15 months. This result is consistent with or better than those reported earlier, including the pivotal phase 3 trials leading to the approval of sunitinib for second-line treatment.[2] In our study, second-line treatment was also associated with longer PFS and OS in the presence

of mutated c-KIT as compared to wild type. However, small numbers limit the interpretation of this finding.

While regorafenib has been approved as third-line therapy in advanced GIST after being compared with placebo, there is no head-to-head comparison with a proven tyrosine kinase inhibitor for regorafenib.[6] In our study, the median OS and median PFS survival with third-line treatment was 12.2 and 8 months, respectively, although multiple options were used. The declining number of patients receiving third-line therapy in comparison to second- and first-line therapy is also an indication of a real-world cohort, where direct application of trial data is not feasible.

This study is not without its inherent pitfalls. The retrospective nature and a relatively small sample size limit the scope of our analysis. The c-KIT mutation status was analyzed on archived FFPE paraffin blocks, and c-KIT mutation data were not available in nearly 50% of our patients. Platelet-derived growth factor receptor alpha mutation status results could not be added as the tests were standardized in recent years at our center.

Conclusion

GIST diagnosed and treated in the Indian subcontinent show improved outcomes. The importance of c-KIT mutation analysis in determining the prognosis and outcomes of patients with advanced GIST is emphasized.

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Conflicts of interest

There are no conflicts of interest.

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