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Ripretinib in Advanced Gastrointestinal Stromal Tumors: A Case Series and Literature Review from a Tertiary Cancer Center in India

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Abstract

The therapeutic armamentarium for advanced gastrointestinal stromal tumors (GISTs) is rapidly evolving and demands personalized strategies due to its increasing complexity. We are witnessing an expansion of the treatment modalities with new molecules being added to the same. Novel agents such as avapritinib and ripretinib have been granted Food and Drug Administration approval for platelet-derived growth factor α-D842V-mutant and refractory GIST patients, respectively. Ripretinib received its approval in May 2020 for individuals with advanced GIST who had been treated with three or more kinase inhibitors after publication of results of the INVICTUS trial. Here, we share our experience of four patients with previously treated advanced GIST who received ripretinib through an expanded access program. Our favorable experience with ripretinib warrants wider availability and easy accessibility of this drug in India for improving outcomes of patients with GIST.

Keywords
- advanced GIST
- ripretinib
- case series

Introduction

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal neoplasms originating in the gastrointestinal tract. Majority (90%) GISTs harbor mutations in either *c-KIT* (~75%) or platelet-derived growth factor α *(PDGFRA)* (10–20%) genes. The approval of imatinib for late-stage GISTs resulted in significant improvement in patient outcomes, with a median progression-free survival (PFS) of approximately 2 years and a median overall survival (OS) of approximately 5 years, with some patients experiencing favorable outcomes for up to 10 years.[1] *c-KIT* exon 9-mutant GISTs may benefit from a higher starting dose of imatinib (800 mg/day) when compared with *c-KIT* exon 11-mutated GIST.[2] Similarly, *PDGFRA*-D842V-mutated and wild-type GISTs remain relatively insensitive to imatinib.[3] For patients who have experienced progression on imatinib, sunitinib and regorafenib are the second- and third-line medications approved by the U.S. Food and Drug Administration (FDA), respectively.[4,5]

Avapritinib is a targeted inhibitor of tyrosine kinases that focuses on *PDGFRA*, including mutations in *PDGFRA*-D842V and *c-KIT* mutations found in exon 11 and exon 17. The FDA granted breakthrough therapy designation for avapritinib, targeting GIST patients that have mutation in exon 18 of *PDGFRA*, which includes D842V mutation. This followed the publication of the NAVIGATOR trial, which displayed

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favorable outcomes in this subset.[6] The overall response rate for *PDGFRA*-mutant GIST ($n = 56$) patients was 88%. The median duration of response was not reached at a median follow-up of 15.9 months.

Ripretinib, a type II tyrosine switch-control inhibitor, exerts its effect by employing a dual mechanism to inhibit kinase signaling. Ripretinib binds selectively and durably to both the switch pocket and the activation loop, stabilizing the kinase in its inactive conformation and thereby blocking downstream signaling and inhibiting cell proliferation. Through its dual mechanism of action, ripretinib broadly inhibits *KIT* and *PDGFRA* kinases, targeting not only the wild-type forms but also a wide range of primary and secondary mutations, including those linked to resistance against other tyrosine kinase inhibitors (TKIs). In vitro studies have shown that ripretinib also inhibits additional kinases, including *PDGFRB*, *TIE2*, *VEGFR2*, and *BRAF*, highlighting its broad-spectrum kinase inhibitory activity.[7]

The initial phase I clinical trial (NCT02571036) explored the potential of ripretinib.[8] The recommended dose as per this study was 150 mg orally once daily. The median PFS was 10.7 months for patients on second-line therapy, 8.3 months for third-line, and 5.5 months for fourth-line or greater therapy.

Its efficacy was demonstrated in the INVICTUS trial, which was a randomized phase 3 trial. A total of 129 patients with advanced GIST were randomized to either ripretinib or placebo. The group receiving ripretinib experienced a median PFS of 6.3 months, whereas the placebo group had a median PFS of 1 month. Median OS was better in the ripretinib arm at 15.1 months versus 6.6 months in the placebo arm. Based on favorable results from this trial, ripretinib was granted FDA approval for advanced GIST in the 4th line.[9] This approval expands the therapeutic options available for GIST further with improvement in clinically relevant outcomes. The most common treatment-related adverse events in patients receiving ripretinib reported in the trial were alopecia, nausea, fatigue, myalgia, hand-foot syndrome (HFS), and diarrhea. Patients progressing on ripretinib were further considered for intrapatient dose escalation (IPDE). Results from IPDE suggested that escalation of ripretinib dose to 150 mg twice a day upon progression on 150 mg once a day may provide additional benefit without compromising safety in GIST patients receiving therapy in the 4th line.[10] Based on demonstration of substantial activity in further lines, the INTRIGUE trial was conducted to demonstrate its activity in second-line GIST, where it was compared with sunitinib.[11]

Despite the FDA approval for ripretinib in 2020, there is paucity of published literature from India regarding its use. This is primarily due to the lack of availability of ripretinib. In this series, we describe our initial favorable experience with ripretinib in four patients treated for advanced GIST in further lines.

This case series evaluated patients with advanced GIST who had progressed postmultiple lines of treatment (median = 3) and were subsequently treated with ripretinib at a dose of 150 mg once daily. Ripretinib was accessed through a compassionate use program. Pathology review of all cases was done by an experienced pathologist specializing in sarcoma pathology. The dose of ripretinib administered (150 mg once daily) was consistent with the dose used in clinical trials concerning ripretinib. The response assessment was done using RECIST 1.1 criteria. Data was extracted from hospital records and included information on patient demographics (age, sex, site), tumor site, site of metastasis, tumor mutational status, prior lines of therapy, clinical outcomes, and treatment responses. Statistical analysis was performed using SPSS 23 (SPSS Inc., Illinois, United States).

Categorical variables are presented as numbers and percentages, while continuous variables are expressed as median with range(s). PFS was defined as the time from initiation of therapy to the date of documented progression or death from any cause.

Case 1

A 19-year-old male was diagnosed with metastatic jejunal GIST. He underwent resection of the primary lesion along with incomplete excision of hepatic metastasis. Postoperatively, he was initiated on imatinib 400 mg daily, which was continued for 3 years, during which he achieved a partial response (PR). Five years after completing therapy, the disease progressed in the liver. Mutation testing revealed *c-KIT* exon 17 mutation. He underwent stereotactic radiosurgery for hepatic metastasis; however, a follow-up positron emission tomography-computed tomography scan at 3 months demonstrated overt radiologic progression, with development of multiple liver and omental metastases. He was initiated on sunitinib, but experienced rapid disease progression within 5 months. Subsequently, he received regorafenib and attained stable disease, although grade 3 toxicities necessitated a dose reduction to 80 mg once a day. He experienced disease progression after 6 months. He was initiated on avapritinib after discussion in the tumor board. He tolerated the drug well with grade II skin toxicity and transaminitis. Although initial imaging at 3 months displayed stable disease, progression was seen at 5 months. He was then initiated on ripretinib at a dose of 150 mg once a day. He tolerated the drug well, experiencing grade 2 HFS and alopecia. He responded clinically with reduction in pain and improvement in appetite. Although a repeat imaging displayed stable disease after 2 months of therapy, he experienced disease progression after 4 months. He received ponatinib after progression on ripretinib.

Case 2

A 47-year-old male was diagnosed with duodenal GIST with hepatic metastasis and initiated on imatinib 400 mg once daily. He developed radiologic disease progression after 2 years of therapy, which was followed by dose escalation to 800 mg once daily. Despite the dose escalation, disease progression occurred within 5 months. Mutation analysis showed *c-KIT* exon 11 mutation. The patient was commenced on sunitinib. Surgical resection of the duodenojejunal tumor

was done along with hepatic metastatectomy. He evidenced disease progression after 1 year. Subsequently, he was initiated on regorafenib but developed disease progression within 4 months, with increase in the size of hepatic lesions along with new skeletal lesions. He was initiated on avapritinib 300 mg once daily. He tolerated the drug well with stable disease for a period of 10 months and later progressed in the liver. Thereafter, he was initiated on ripretinib 150 mg once a day through compassionate access program. He tolerated the drug well along with symptomatic improvement and a radiologic PR as shown in ►**Fig. 1**. His disease progressed after 6 months with increasing liver lesions, peritoneal deposits, and skeletal metastases. Subsequently, he was initiated on cabozantinib at a dose of 60 mg once daily.

Case 3

A 45-year-old female diagnosed with high-risk jejunal GIST underwent wide local excision of jejunal mass and anastomosis at an outside facility. She was initiated on imatinib 400 mg once daily. She remained in complete response after 1 year of treatment and imatinib was discontinued thereafter at an outside institution. She progressed after 1 year with peritoneal and omental metastasis and presented to our clinic. She was rechallenged with imatinib, achieving a PR which was maintained for 5 years. Imatinib dose was escalated to 800 mg once daily upon progression. However, she progressed within 3 months. She was switched to sunitinib 37.5 mg once daily and achieved PR, which was maintained for a duration of 3 years. Upon progression, she was initiated on regorafenib. However, it had to be discontinued within 4 months due to poor tolerance and grade 3 toxicities. Thereafter, she was started on ripretinib 150 mg once daily and achieved stable disease with good tolerance. She evidenced radiologic progression in the liver and pelvic area after 6 months. At this point, ripretinib dose escalation was done to 150 mg twice daily, resulting in 2 months of additional disease control. Therapy was discontinued thereafter due to the drug unavailability owing to the coronavirus disease 2019 (COVID-19) pandemic. She later progressed and was rechallenged with imatinib as per the RIGHT[12] trial but she eventually succumbed to her illness.

Case 4

A 54-year-old male presented with a large ulceroproliferative gastric GIST arising from the fundus and body of the stomach, closely abutting the splenic hilum, with radiologically evident metastases to abdominal lymph nodes and hepatic parenchyma. His baseline mutation testing was not available. He received imatinib 400 mg for 6 months followed by palliative radical gastrectomy with splenectomy at an outside institution. He developed abdominal wall recurrence after 8 months, which was managed with excision and small bowel resection. Over the next several years, he developed multiple hepatic recurrences requiring hepatic segmentectomies.

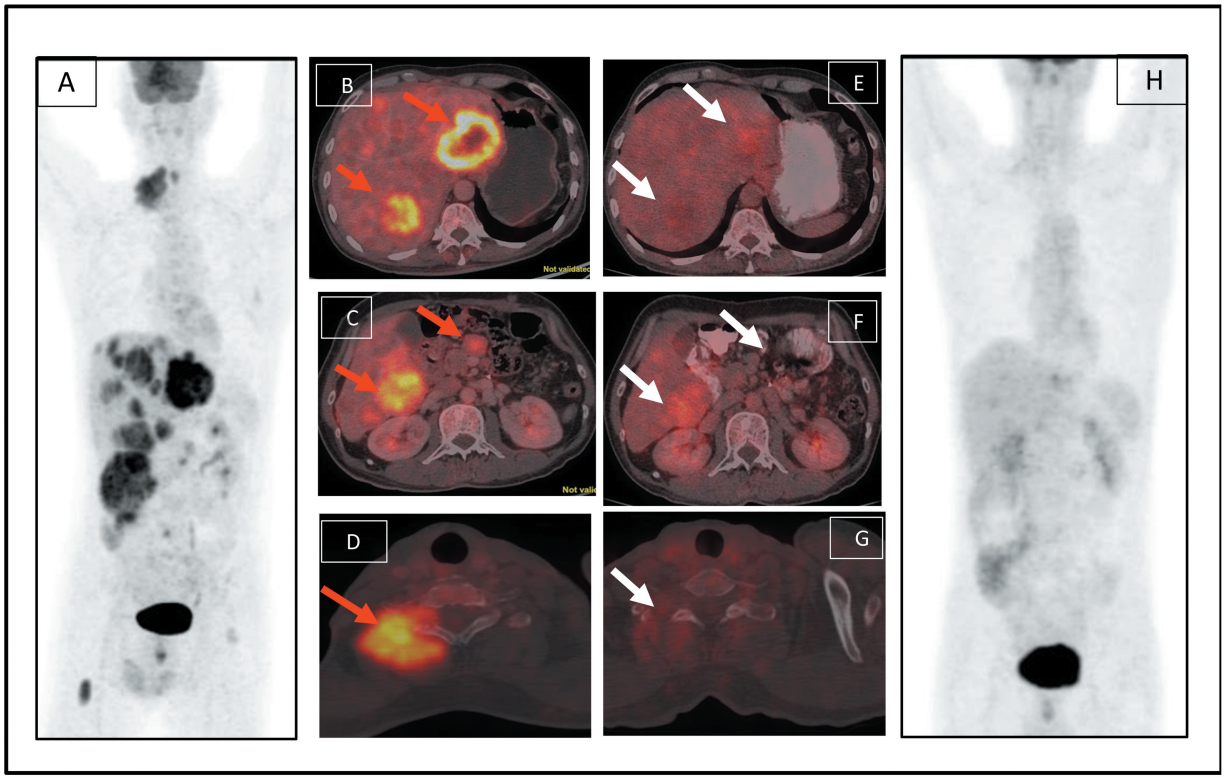

Fig. 1 Baseline fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) (**A–D**) images show tracer-avid liver lesions, mesenteric nodes, and lytic lesion in D1 vertebra (red arrows). Follow-up scan post-3 months of ripretinib treatment (**E–H**) shows decreased tracer uptake and lesions size (white arrows), indicating partial response.

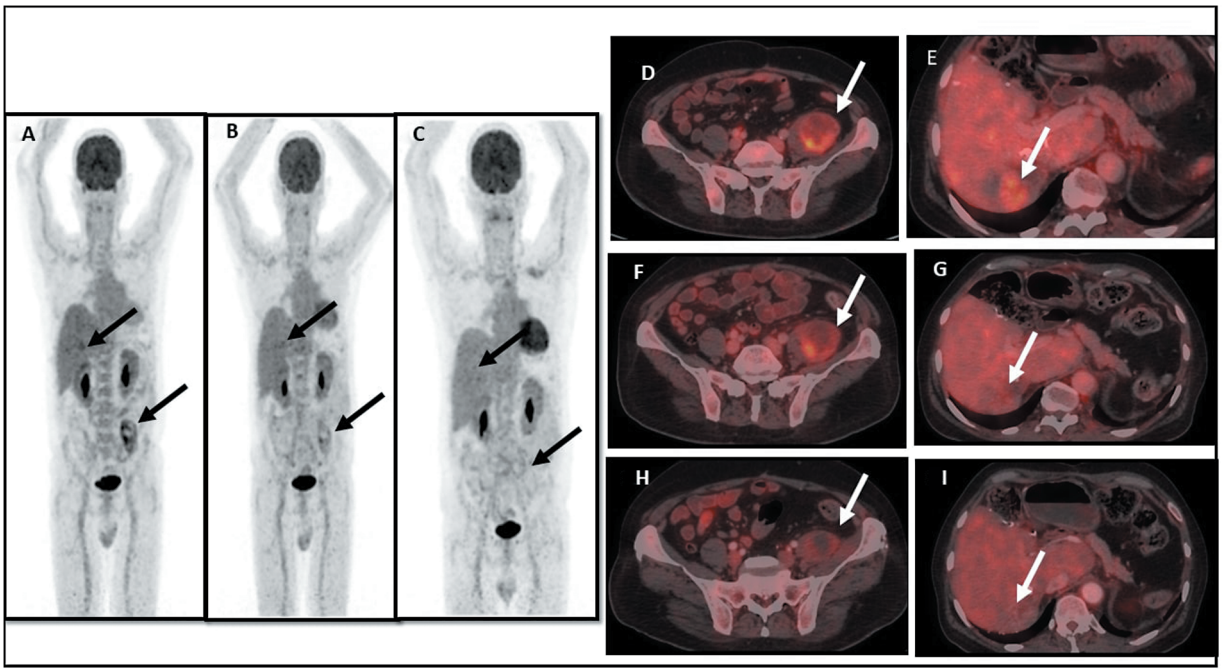

Fig. 2 Serial fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) images of pretreatment (**A**, **D**, **E**) post-3 months of ripretinib (**B**, **F**, **G**) showing partial response and post-7 months of treatment (**C**, **H**, **I**) showing stable disease in liver lesions and psoas muscle deposit (white and black arrows).

Mutation analysis during this time showed *c-KIT* exon 11 and 17 mutations. Upon further progression he was referred to our institution. He was initiated on second-line sunitinib and underwent radiofrequency ablation to liver lesion. He had rapid progression within 4 months requiring initiation of third-line regorafenib. Regorafenib dose escalation from 80 mg/120 mg alternate day to 120 mg daily failed to prevent progression of the disease with new lesions in the liver and psoas muscle. Transarterial chemoembolization was done for the hepatic lesions followed by initiation of ripretinib 150 mg daily. Stereotactic body radiotherapy was done for the psoas muscle deposit. The patient achieved PR at 3 months as shown in ►**Fig. 2**. Later, he maintained stable disease for a duration of 7 months. Subsequently, he developed hepatic progression at 10 months. He also developed heart failure secondary to ripretinib, which required intensive care unit admission and drug discontinuation. He was later reintroduced on imatinib as per the RIGHT trial.[12]

Baseline Characteristics

The baseline characteristics and mutation profiling of the patients are summarized in ►**Table 1**.

Ripretinib Efficacy and Safety

►**Table 2** depicts our clinical experience with the use of ripretinib. The best response observed was PR (2 out of 4 patients) and stable disease in the other two patients. Disease progression was seen in all the patients of this cohort. Three patients had disease progression while on

Table 1 Baseline characteristics of patients

Case	Age/sex	Primary site	Mutation analysis	Previous therapies received and best response	Sites of metastases
1	19/ M	Jejunum	cKIT exon 17	Imatinib (PR) Sunitinib (PD) Regorafenib (SD) Avapritinib (SD)	Liver, omental deposits
2	47/ M	Duodenum	cKIT Exon 11	Imatinib (PR) Sunitinib (SD) Regorafenib (PD) Avapritinib (SD)	Liver, omental deposits, peritoneal deposits, skeletal lesions, mesenteric lymph nodes
3	45/ F	Jejunum	cKIT exon 11	Imatinib (CR) Sunitinib (PR) Regorafenib (stopped due to intolerance)	Liver, peritoneal deposits and mesenteric deposits
4	54/ M	Gastric	cKIT Exon 11 + 17	Imatinib (PR) Sunitinib (SD) Regorafenib (SD)	Liver, psoas muscle deposit

Abbreviations: CR, complete response; F, female; M, male; PD, progressive disease; PR, partial response; SD, stable disease

Table 2 Treatment response, progression-free survival, and adverse events with ripretinib in patients with advanced GIST

Case	Dose	Response	PFS	Post-Ripretinib therapy	Grade 2 toxicities	Grade 3 toxicities
1	150 mg once daily	SD at 2 months followed by PD at 4 months	4 months	Ponatinib	Alopecia, HFS, anemia, fatigue	None
2	150 mg once daily	PR at 3 months followed by PD at 6 months	6 months	Cabozantinib	HFS	None
3	150 mg once daily for 6 months, 150mg twice daily for 2 months	SD at 3 months followed by PD 3 months later, did IPDE which yielded 2 months PFS	8 months	Imatinib	Alopecia, myalgias, fatigue	None
4	150 mg once daily	PR after 3 months, SD till 7 months followed by PD at 10 months	10 months	Imatinib	Alopecia	Left- ventricular dysfunction

Abbreviations: GIST, gastrointestinal stromal tumor; HFS, hand-foot syndrome; IPDE, intrapatient dose escalation; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

ripretinib. One patient (case 3) could not receive further ripretinib due to the COVID-19 pandemic and progressed after drug discontinuation. The median PFS was 6 months on ripretinib (range: 4–10) (►**Fig. 3**).

Ripretinib was generally well tolerated. All four evaluable patients experienced grade 2 toxicities, and one patient developed a grade 3 adverse event (left ventricular dysfunction requiring hospitalization). The most commonly reported toxicity was alopecia ($n = 3$; 75%). Grade 2 fatigue and HFS were observed in two patients each (50%). Notably, none of the patients required dose interruptions. Ripretinib had to be discontinued in one patient due to further unavailability of the drug.

Discussion

Advanced GISTs continue to pose therapeutic challenges, especially beyond first-line therapy. Despite the use of sunitinib and regorafenib in the second- and third-line settings, these agents demonstrate declining efficacy over time due to the emergence of resistant mutations. The approvals of avapritinib and ripretinib have significantly expanded the therapeutic landscape, offering new hope for patients with refractory disease. Ripretinib is a novel "switch-control" TKI targeting a broad spectrum of KIT and *PDGFRA* mutations. It received FDA approval in May 2020 for use in patients with advanced GIST who have progressed on

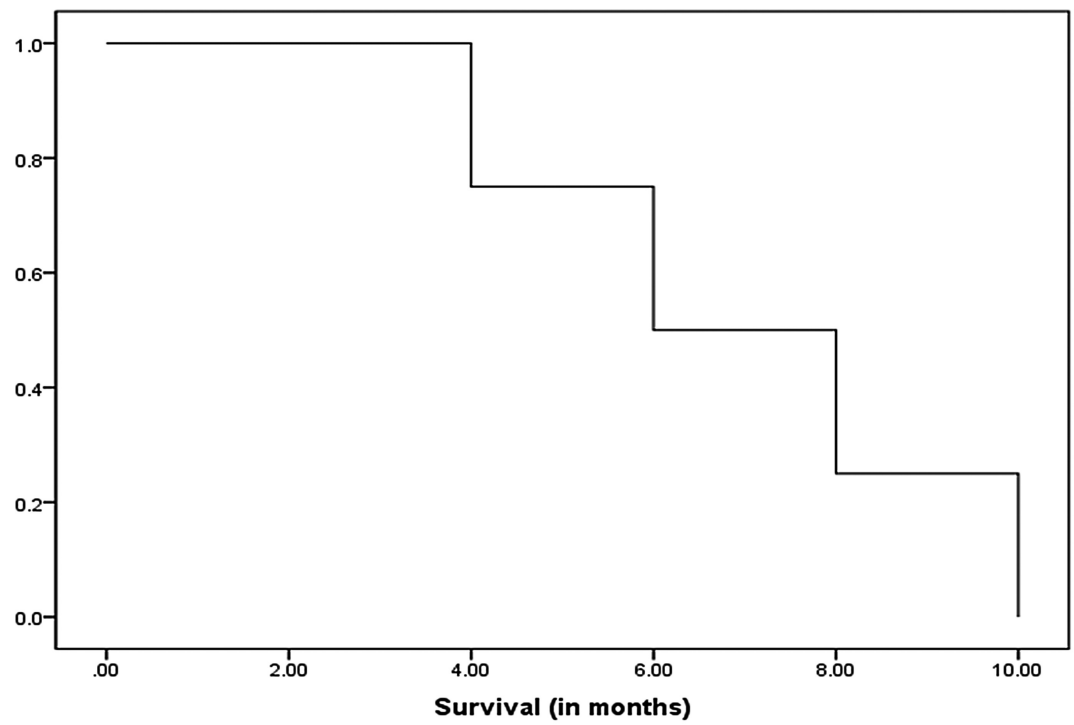

Fig. 3 Progression-free survival (PFS).

at least three prior TKIs, including imatinib, sunitinib, and regorafenib. However, despite FDA approval, ripretinib remains largely inaccessible in certain parts of the world, including most of the low-middle income countries. This highlights a critical need for wider access to the drug. In this report, we presented our clinical experience of four heavily pretreated patients with advanced GIST who received ripretinib in India through a compassionate access program. We demonstrated favorable efficacy with ripretinib and an acceptable safety profile in this cohort.

In our case series, patients had a median age of 50.5 years and had received a median of three prior lines of therapy before initiation of ripretinib. All had a significant disease burden and derived clinical benefit from the drug. The median PFS in our cohort was 6 months, which closely aligns with 6.3 months reported in the INVICTUS trial.[9] In our cohort, three patients developed alopecia (75%), two experienced fatigue (50%), and two had HFS (50%). Other notable adverse effects included myalgias and anemia. One patient developed grade 3 left ventricular dysfunction requiring hospitalization. Two of the four patients had previously received avapritinib through compassionate access prior to the availability of NAVIGATOR trial data. The INVICTUS trial permitted IPDE of ripretinib.[10] Among 43 patients on IPDE, median PFS1 and PFS2 were 4.6 and 3.7 months, respectively; median OS was 18.4 months. Ripretinib 150 mg twice daily was well tolerated. Grade 3 to 4 adverse events included anemia (14%) and abdominal pain (7%); 16% discontinued due to toxicity. The strategy showed potential benefit with manageable safety. In our series, one patient received dose escalation, which resulted in an additional PFS benefit of 2 months without significant added toxicity.

Molecular profiling in our cohort revealed KIT exon 11 mutations in three patients and exon 17 mutations in two, with one being a secondary resistance mutation. There is increasing recognition of the mutation-specific activity of ripretinib, especially in the context of emergence of secondary mutations. The INTRIGUE trial, which was a randomized phase III trial, compared ripretinib with sunitinib as second-line therapy with advanced GIST.[11] In this trial, ripretinib demonstrated a higher objective response rate (23.9% vs. 14.6%, $p = 0.03$) and better tolerability (grade ¾ treatment emergent adverse effects (TEAEs): 41.3% vs. 65.6%) compared with sunitinib in *KIT* exon 11-mutant GIST. However, overall PFS was similar (8.0 vs. 8.3 months), and no PFS superiority was seen in the intention-to-treat population. An exploratory circulating tumor DNA (ctDNA) analysis from the INTRIGUE trial showed mutation-specific responses: patients with *KIT* exon 11 + 13/14 mutations benefited more from sunitinib (PFS: 15.0 vs. 4.0 months), while those with exon 11 + 17/18 mutations responded better to ripretinib (PFS: 14.2 vs. 1.5 months).[13] These findings underscore the potential utility of ctDNA in guiding therapy for GIST.

These data paved the way for the ongoing INSIGHT trial, the first phase III study using ctDNA-based selection, which is evaluating ripretinib versus sunitinib in *KIT* exon 11 + 17/18 mutations. Results expected by 2027 may validate ctDNA as a noninvasive tool for therapy selection, especially when tissue biopsy is not feasible.[14]

Strengths and Limitations

Strengths of our study include its real-world nature and being the index Indian case series highlighting ripretinib use in the subcontinent. However, limitations include its small sample size, retrospective design, and absence of patient-reported outcome data. Future research should focus on ctDNA-guided therapy algorithms and also on patient-reported outcomes and safety analysis. This case series also highlights the practical challenges in accessing novel effective treatment options and provides pragmatic insights into use of such novel agents like ripretinib in low-resource settings.

Conclusion

In our study, the efficacy and safety profile of ripretinib in later lines for patients with advanced GIST from India closely mirror the outcomes reported in pivotal trials like INVICTUS. The introduction of newer agents has brought renewed hope to the management of advanced GIST. Real-world experience like these will guide clinical decision-making and reinforce invaluable utility of such agents. Moving forward, it is imperative to expand access to drugs like ripretinib for patients from low-middle income countries to help reduce global disparities in cancer care and improve outcomes.

Note

The manuscript has been read and approved by all the authors and each author believes that the manuscript represents honest work.

Authors' Contributions

The concept, design, and manuscript review were carried out by S.R. Literature search, statistical analysis, and manuscript preparation were performed by V.N. Manuscript preparation was additionally contributed by M.S.B. and S.A.S., while S.S. was responsible for manuscript editing and review.

Patients' Consent

Verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report have been obtained.

Conflict of Interest

None declared.

Acknowledgments

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References

1 Blay JY. A decade of tyrosine kinase inhibitor therapy: historical and current perspectives on targeted therapy for GIST. Cancer Treat Rev 2011;37(05):373–384

2 Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST) Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 2010;28(07): 1247–1253

3 Gounder MM, Maki RG. Molecular basis for primary and secondary tyrosine kinase inhibitor resistance in gastrointestinal stromal tumor. Cancer Chemother Pharmacol 2011;67 (Suppl 1, Suppl 1):S25–S43

4 Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368(9544):1329–1338

5 Demetri GD, Reichardt P, Kang YK, et al; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381(9863): 295–302

6 Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced *PDGFRA* D842V- mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol 2020;21(07):935–946

7 Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. Cancer Cell 2019;35 (05):738–751.e9

8 Janku F, Abdul Razak AR, Chi P, et al. Switch control inhibition of KIT and PDGFRA in patients with advanced gastrointestinal stromal tumor: a phase I study of ripretinib. J Clin Oncol 2020; 38(28):3294–3303

9 Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo- controlled, phase 3 trial. Lancet Oncol 2020;21(07):923–934

10 Zalcberg JR, Heinrich MC, George S, et al. Clinical benefit of ripretinib dose escalation after disease progression in advanced gastrointestinal stromal tumor: an analysis of the INVICTUS study. Oncologist 2021;26(11):e2053–e2060

11 Bauer S, Jones RL, Blay JY, et al. Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE): a randomized, open-label, phase III trial. J Clin Oncol 2022;40(34):3918–3928

12 Kang YK, Ryu MH, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14(12):1175–1182

13 Heinrich MC, Jones RL, George S, et al. Ripretinib versus sunitinib in gastrointestinal stromal tumor: ctDNA biomarker analysis of the phase 3 INTRIGUE trial. Nat Med 2024;30(02):498–506

14 George S, Blay JY, Chi P, et al. The INSIGHT study: a randomized, Phase III study of ripretinib versus sunitinib for advanced gastrointestinal stromal tumor with *KIT* exon 11 + 17/18 mutations. Future Oncol 2024;20(27):1973–1982

