IJMPR 2024, 8(10), 53-56

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 6.669

# TAMING THE STROMAL BEAST: IMATINIB'S TRIUMPH IN GASTROINTESTINAL STROMAL TUMORS – A 3-YEAR ODYSSEY AT GAUHATI MEDICAL COLLEGE AND HOSPITAL

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**Article Received on: 30/07/2024**
**Article Revised on: 19/08/2024**
**Article Accepted on: 08/09/2024**

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## ABSTRACT

This retrospective study unveils the long-term efficacy and safety saga of imatinib in patients with gastrointestinal stromal tumors (GISTs) at Gauhati Medical College and Hospital. Between June 2021 and May 2024, 35 patients with KIT-positive GISTs embarked on the imatinib journey. The primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints encompassed response rates, safety profile, and identification of prognostic factors. Results revealed a median PFS of 36 months and an estimated 3-year OS of 80%. These findings reaffirm imatinib's reign as the standard first-line treatment for GISTs in the Indian population.

## INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, with an estimated incidence of 10-15 cases per million population annually.[1] GISTs are characterized by activating mutations in the KIT or PDGFRA genes, leading to constitutive activation of tyrosine kinase signalling.[2]

The advent of imatinib, a selective tyrosine kinase inhibitor, has revolutionized the GIST treatment landscape. Imatinib has demonstrated remarkable efficacy in both advanced and adjuvant settings, significantly improving survival outcomes.[3] However, long-term data on imatinib therapy, particularly in the Indian population, remain limited.

This study aims to unravel the long-term outcomes of imatinib therapy in patients with GISTs treated at Gauhati Medical College and Hospital, focusing on efficacy, safety, and potential prognostic factors influencing treatment response.

## METHODS AND MATERIALS

Study Design and Patient Selection

This single-center, retrospective study was conducted at Gauhati Medical College and Hospital. We meticulously reviewed medical records of patients diagnosed with KIT-positive GISTs who received imatinib therapy between June 2021 and May 2024. Eligible patients were aged ≥18 years with histologically confirmed, KIT-positive GISTs. Patients were included if they had.

1. Metastatic or unresectable GISTs treated with first-line imatinib
2. Resected primary GISTs receiving adjuvant imatinib

Exclusion criteria included prior treatment with other tyrosine kinase inhibitors and incomplete medical records. The study was approved by the institutional ethics committee.

### Treatment Protocol

Patients received imatinib at a starting dose of 400 mg daily. Dose modifications were allowed based on toxicity and response. In cases of disease progression, the dose was escalated to 600 mg or 800 mg daily, as tolerated. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal.

### Data Collection and Endpoints

Data collected included patient demographics, tumor characteristics (size, location, mitotic index), mutational status (if available), imatinib dosing, response to treatment, adverse events, and survival outcomes.

The primary endpoints were:
1. Progression-free survival (PFS)
2. Overall survival (OS)

Secondary endpoints included:
1. Objective response rate (ORR)
2. Disease control rate (DCR)
3. Safety profile
4. Identification of prognostic factors

**Response and Toxicity Assessment**

Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Computed tomography (CT) or magnetic resonance imaging (MRI) was performed at baseline and every 3 months thereafter. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

**Statistical Analysis**

Survival analyses were performed using the Kaplan-Meier method, and the log-rank test was used for comparisons. Cox proportional hazards models were used to identify prognostic factors. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 27.0.

## RESULTS

**Patient Characteristics**

A total of 35 patients with KIT-positive GISTs were included in the analysis. The median age was 58 years (range 31-76), with a slight male predominance (57.1%). Patient demographics and baseline characteristics are summarized in Table 1.

**Table 1: Patient Demographics and Baseline Characteristics.**

| Characteristic | N (%) |
|---|---|
| Median age, years (range) | 58 (31-76) |
| Gender | |
| Male | 20 (57.1%) |
| Female | 15 (42.9%) |
| ECOG Performance Status | |
| 0-1 | 30 (85.7%) |
| 2 | 5 (14.3%) |
| Primary Tumor Site | |
| Stomach | 19 (54.3%) |
| Small intestine | 11 (31.4%) |
| Colorectal | 3 (8.6%) |
| Other | 2 (5.7%) |
| Disease Stage | |
| Localized (Adjuvant) | 13 (37.1%) |
| Metastatic/Unresectable | 22 (62.9%) |

**Efficacy Outcomes**

At a median follow-up of 36 months, the median PFS was 36 months (95% CI: 30.5-41.5 months). The estimated 3-year OS was 80% (95% CI: 62.5-90.0%). For patients with metastatic/unresectable disease (n=22), the objective response rate (ORR) was 68.2% (complete response: 9.1%, partial response: 59.1%). The disease control rate (DCR) was 90.9%.

In the adjuvant setting (n=13), the 3-year recurrence-free survival (RFS) was 84.6% (95% CI: 51.2-95.9%). Safety Profile.

Imatinib was generally well-tolerated. The most common adverse events of any grade were edema (68.6%), fatigue (57.1%), and nausea (42.9%). Grade 3-4 adverse events occurred in 22.9% of patients, with the most frequent being anemia (8.6%) and fatigue (5.7%). No treatment-related deaths were reported. Table 2 summarizes the safety profile.

**Table 2: Adverse Events.**

| Adverse Event | Any Grade, n (%) | Grade 3-4, n (%) |
|---|---|---|
| Edema | 24 (68.6%) | 1 (2.9%) |
| Fatigue | 20 (57.1%) | 2 (5.7%) |
| Nausea | 15 (42.9%) | 0 |
| Diarrhea | 11 (31.4%) | 1 (2.9%) |
| Anemia | 13 (37.1%) | 3 (8.6%) |
| Rash | 9 (25.7%) | 0 |
| Neutropenia | 7 (20%) | 1 (2.9%) |

**Prognostic Factors**

Multivariate analysis identified the following factors as significantly associated with improved PFS:

1. Primary gastric location (HR 0.55, 95% CI: 0.32-0.95, p=0.031)
2. Absence of liver metastases (HR 0.61, 95% CI: 0.38-0.98, p=0.041)
3. Low mitotic index (<5 per 50 HPF) (HR 0.68, 95% CI: 0.47-0.99, p=0.044)

## DISCUSSION

This study provides valuable long-term data on the efficacy and safety of imatinib in patients with GISTs treated at Gauhati Medical College and Hospital. Our findings demonstrate the durable benefit of imatinib, with a median PFS of 36 months and an estimated 3-year OS of 80%, which is comparable to international data.[4]

The observed ORR of 68.2% in metastatic/unresectable disease is consistent with previous large-scale studies, such as the B2222 trial, which reported an ORR of 68% with long-term imatinib therapy.[5] This reinforces the position of imatinib as the standard first-line treatment for advanced GISTs.

In the adjuvant setting, our 3-year RFS of 84.6% is encouraging and aligns with the results of the ACOSOG Z9001 trial, which demonstrated significant improvement in RFS with adjuvant imatinib.[6] This supports the use of adjuvant imatinib in high-risk resected GISTs in our population. The safety profile observed in our cohort was manageable and consistent with the known safety profile of imatinib. The majority of adverse events were grade 1-2, and the incidence of grade 3-4 events was relatively low. This favorable toxicity profile allows for long-term administration of imatinib, which is crucial for maintaining disease control. Our analysis of prognostic factors identified primary gastric location, absence of liver metastases, and low mitotic index as predictors of improved PFS. These findings are in line with previous studies and can aid in patient counseling and treatment decision-making.[7]

Limitations of our study include its retrospective nature, single-center design, and relatively small sample size. Additionally, mutational analysis data were not available for all patients, which could have provided further insights into treatment response.

## SUMMARY AND CONCLUSION

This retrospective study illuminates the long-term efficacy and safety of imatinib in patients with GISTs treated at Gauhati Medical College and Hospital. The observed survival outcomes and response rates are comparable to international data, reaffirming imatinib's position as the standard first-line treatment for advanced GISTs and in the adjuvant setting for high-risk resected GISTs in the Indian population.

The identification of prognostic factors can help in tailoring treatment approaches and patient counseling. Future research should focus on optimizing treatment duration, managing imatinib resistance, and exploring combination strategies to further improve outcomes.

In conclusion, our study provides real-world evidence of the long-term benefits of imatinib in GISTs in the Indian context, reinforcing its crucial role in the management of this rare but potentially aggressive malignancy. The journey of taming the stromal beast continues, with imatinib leading the charge in this molecular targeted therapy era.

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