TREATMENT OUTCOME FOLLOWING IMATINIB IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMOUR (GIST) IN KHYBER PAKHTUNKHWA, PAKISTAN

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ABSTRACT

Objective: Gastrointestinal stromal tumours (GIST) are rare tumours of gastrointestinal tract. The association of their characteristics with patient survival are poorly defined. A risk stratification is critical to optimize the treatment strategy despite an improved survival with adjuvant therapies, such as Imatinib. We aimed to identify the risk factors and treatment outcome of GIST patients.

Methodology: We evaluated the demography and disease characteristics of patients with GIST presenting to Hayatabad Medical Complex (HMC), Peshawar, Pakistan. The diagnostic criteria included characteristic morphology and CD117/DOG-1 positivity. We performed pre- and post-surgical CT scans and treated patients with metastatic disease or high-risk factors with daily Imatinib of 400–800 mg.

Results: A total of 221 GIST patients with CD117/DOG1 positive tumours presented to Hayatabad Medical Complex (HMC) between January 2015 and February 2023. 150 (67.87%) patients were male while 71 (32.33%) patients were female. Median age at the time of diagnosis was 50 years (range 17–75 years). Commonest site at presentation was stomach in 120 (54.30%) patients, small intestine in 60 (27.15%) patients, colorectal in 20 (9.05%) patients and other cases were 21 (9.50%). Tumor size was 2cm or less in 18(8.14%) patients, > 2 - ≤5 cm in 24 (10.86%) patients, >5cm - ≤10cm in 68 (30.77%) patients while 93 (42.09%) patients had tumors >10 cm. In 18 (8.14%) patients, tumor size at presentation was unknown. Mitotic count/50 HPF was ≤5 in 90 (40.73%) tumors and >5 in 102 (46.15%) tumors. Mitotic Count was not reported in 29 (13.12%) biopsies.

Conclusion: We report an earlier age at onset in our region than most Western countries. Most of our patients had aggressive disease features. Response to Imatinib was found to be satisfactory while treatment was well tolerated.

Keywords: GIST, Gastrointestinal stromal tumours, Imatinib, treatment, risk factors, prognosis.

INTRODUCTION

Gastrointestinal stromal tumours (GIST) exhibit a mesenchymal origin and constitute <1% of all gastrointestinal (GI) cancers[1,2]. According to current epidemiology, the annual incidence of GIST in the United States is 0.68-0.78 per 100,000 people, with an increasing tendency annually[3]. GIST originate from interstitial cells of Cajal and are known to show reactivity to the c-kit receptor (cluster of differentiation 117 CD117).

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Apart from CD117 positivity on immunohistochemistry, these tumours also show positivity to (cluster of differentiation 34 CD34)[4,5] Diagnosed on gastrointestinal stromal tumors (DOG1) antibody exhibits a higher sensitivity than c-kit with an expression of 36% in c-kit negative GISTs. DOG 1 is therefore currently part of immunohistochemical markers used in diagnosis of GIST [6,7].

Recent research has shown that mutations in the receptor tyrosine kinase (KIT) gene, among other genes, are linked with the response to Imatinib [8]. These frequent mutations have evolved into an important component of the GIST management [9]. The annual incidence of GIST ranges from 10 to 20 patients per million population [10]. The median age at diagnosis varies from 60 to 65 years. Among GI components, stomach is the commonest site of presentation (50-60%), while small intestine (30%) and colorectal region (5%) may also exhibit GIST [11,12]. Since GIST can behave as low risk or benign tumours to high risk and aggressive behaviour, therefore risk stratification is considered an important part of pre-treatment strategy. Risk stratification for GIST is performed based on site, size, and mitotic index of the tumour [13]. Tumour genotype has not been found to affect survival of GIST patients [14].

Most of the relevant data is from European and American continents. However, similar studies from Indian subcontinent are scarce and partly

elusive. In addition, these studies report inconsistent data about the median age, male to female ratio, and frequency of presentation. We aimed to overcome this problem by conducting a prospective analysis to examine the demographic profile and treatment of GIST patients in Northern Pakistan.

METHODOLOGY

We conducted prospective analysis of patients diagnosed with GIST at the Medical Oncology Department at Hayatabad Medical Complex (HMC), Peshawar. This centre is the main referral centre for all GIST patients diagnosed in northern province of Pakistan, Khyber Pakhtunkhwa, and provides free Imatinib to all patients. Eligibility criteria for patients enrolled in the study was age over 18 years, having confirmed histological and immunohistochemical (IHC) diagnosis of GIST, no history of psychiatric disorder, no history of congestive cardiac failure, myocardial infarction in the previous six months or other severe uncontrolled disease (e.g renal impairment or renal failure), no intolerance to Imatinib and a follow up of at least three months. Patients were enrolled between January 2015 and February 2023. Some patients were started on Imatinib mesylate treatment before 2015 at other centres and were referred to our centre in 2015 after being declared focal point for treating GIST patients in January 2015.

The diagnosis was confirmed by histopathology and staining with cluster of differentiation117 and or diagnosed on gastrointestinal stromal tumors-1 (CD117 and/or DOG-1). We also performed pre and postoperative CT scans along with follow-up ultrasounds. Age, gender, geographic location, type of surgery, size and site of primary tumour, mitotic index of the tumour, metastases at presentation and type of treatment (neo-adjuvant/adjuvant) were noted for all patients. Patients were treated initially with Imatinib Mesylate 400 mg/day. Dose of Imatinib Mesylate was increased to 800 mg daily in patients not responding to initial dose. Risk stratification criteria for classifying GISTs into low, intermediate, and high risk groups proposed by Joensuu et al was adopted [14]. We measured the progression free survival (PFS) from the day-1 of the treatment with Imatinib to progression of disease or death. Overall survival (OS) was measured from the day of start of treatment with Imatinib till death of the patient.

The study was conducted after obtaining an ethics approval from the Hospital Research & Ethics Committee (IREB) of Hayatabad Medical Complex, Peshawar. We obtained informed consent and maintained anonymity of all patients. This study was conducted under the Helsinki Declaration.

The characterization of tumour, including site, size, mitotic count, and response to treatment are reported in percentage prevalence. We used Kaplan-Meier survival analysis to investigate the progression free survival (PFS) and overall survival (OS). For statistical analysis IBM, SPSS 23.0 was used.

RESULTS

Total 221 GIST patients with CD117/DOG1 positive tumours were enrolled. There were 150 (67.87%) male while 71 (32.33%) patients were female with a male to female ratio of 2.1:1. Median age at the time of diagnosis was 50 years (range 17–75 years). Commonest site at presentation was stomach in 120 (54.30%) patients, small intestine in 60 (27.15%) patients, colorectal in 20 (9.05%) patients and other cases were 21 (9.50%).

Tumor size was 2cm or less in 18(8.14%) patients, > 2 - ≤5 cm in 24 (10.86%) patients, >5cm - ≤10cm in 68 (30.77%) patients while 93 (42.09%) patients had tumors >10 cm. In 18 (8.14%) patients, tumor size at presentation was unknown. Median size of the primary tumor at diagnosis was 11±5.29 cm (range 3-25). Mitotic count/50 HPF was ≤5 in 90 (40.73%) tumors and >5 in 102 (46.15%) tumors.

Mitotic Count was not reported in 29 (13.12%) tumors

Total 39 (17.65%) patients had metastatic disease at diagnosis. Sites of metastatic disease at diagnosis were liver 27(69.2%), mesentery 7(17.9%) and lungs 5(12.8%).

Table-1

Details	Frequency	Percentage
Male	150	67.87%
Female	71	32.33%
Stomach	120	54.30%
Intestine	60	27.15%
Colorectal	20	9.05%
Others (peritoneum, mesentry, omentum, esophagus)	21	9.50%
Tumour size		
≤ 2 cm	18	8.14%
>2 - ≤5 cm	24	10.86%
>5 - ≤ 10 cm	68	30.77%
>10cm	93	42.09%
Unknown Tumor Size	18	8.14%
Median size (mean±SD)	11 ± 5.29 cm	
Mitotic count/50 HPF		
≤5	90	40.73%
>5	102	46.15%
Unknown Mitotic count	29	13.12%
Site		
Liver	27	69.2%
Mesentery	7	17.9%
Lungs	5	12.8%

Table 1: demographic details and other characteristics

Data on response to treatment was available for 221 patients. 148 (66.97%) patients had complete response, 6 (2.71%) patients had partial response, 28 (12.67%) patients had stable disease while 39 (17.65%) patients had progressive disease. Dose was increased from 400 mg/day to 800 mg/day in 39 (17.65%) patients while 5 patients were switched to sunitinib due to lack of response at 800 mg/day, after re-evaluation with CT Scans at 3 months. We observed the death of 39 (17.65%) patients with a median period of 36 months from baseline (Table 2).

Outcome	Frequency	Percentage
Complete response	148	67.97%
Partial response	6	2.71%
Stable disease	28	12.67%
Progressive disease	39	17.65%
Mortality	39	17.65%

Table 2: Treatment outcome & mortality

DISCUSSION

Gastrointestinal stromal tumors (GISTs) represent a noteworthy neoplastic entity, with global incidence variations. The reported incidence is 1.0 per 100,000 population in Europe and USA, contrasting with the higher rates of 1.6-2 observed in China and Korea. The diagnosis and subsequent incidence of GIST have notably increased post-2001, primarily attributed to the introduction of CD117 antibodies for diagnosis and the incorporation of the tyrosine kinase inhibitor Imatinib Mesylate for treatment[13,14].

Current recommendations for advanced GIST involve sequential first- and second-line systemic therapy, including Imatinib, avapritinib and sunitinib, followed by third-line therapies, such as regorafenib, riperitinib, pazopanib, sorafenib, or nilotinib. The usage of Imatinib in patients with intermediate or high-risk tumors has significantly impacted outcomes, reduced recurrence rates and improving survival following surgical excision[15,16].

Our center, serving as the primary referral center for GIST patients in Khyber Pakhtunkhwa, Northern Pakistan, conducted an evaluation of 221 patients over 8-years period. The median age of patients (50 years) in our study was lower than that reported in Western literature (50-70 years), with a notable proportion (21%) below the age of 40. The male-to-female ratio in our study was 2.1:1, aligning with a regional study by Siddiqui et al, who report a median age of 50-56 years with 60-65% cases reported in men[17].

Stomach involvement was predominant in our study (54.3%), followed by the small intestine (27.15%) and colon (9.05%), consistent with published data[18]. Tumor size exceeding 10 cm was observed in 42.08% of patients, with a mean tumor size of 11 cm, mirroring regional findings[19]. High mitotic count (> 5) was present

in 46.15% of patients, correlating with adverse prognostic implications.

Metastatic presentation occurred in 17.65% of our patients, primarily in the liver. Our findings and regional studies indicate aggressive disease features at diagnosis, emphasizing the importance of considering adjuvant treatment[20]. Adjuvant Imatinib therapy at 400 mg/day for a median period of 36 months resulted in a complete response in 148 patients and partial response in 4 patients. 41 patients required an increased dose to 800 mg/day, with 36 patients had successful responses. Five patients unresponsive to the higher dose were switched to sunitinib, exhibiting a six-month response before developing resistance.

Our study demonstrated a progression-free survival and overall survival rate of 82.35% after a median follow up of 36 months, aligning with outcomes reported in other trials for intermediate and advanced disease[21,22]. The reasons behind the aggressive disease presentation in our population remain unknown, necessitating further investigation into potential genetic factors.

LIMITATIONS

Several limitations need to be acknowledged. Firstly, the study was conducted at a single center, which may limit the generalizability of findings to other regions or healthcare settings. Additionally, the sample size of 221 patients over an 8-year period, while considerable, may not be sufficient to capture the full spectrum of GIST presentations and outcomes. Moreover, incomplete data for some patients, such as missing tumor size and mitotic count information, may impact the accuracy and comprehensiveness of the analysis. The median follow-up period of 36 months may not fully capture long-term outcomes and recurrence rates. Addressing these limitations in future research endeavors is crucial for a comprehensive understanding of GIST epidemiology and management in Pakistan and beyond.

CONCLUSION

In conclusion, our study underscores unique characteristics of GIST presentation in the Indo-Pakistan subcontinent, including a relatively earlier age of onset and larger tumor size with higher mitotic counts. Despite these differences, treatment outcomes with Imatinib closely parallel those reported in other populations with advanced-stage GIST. Further research is required to explore the potential role of genetic factors in disease presentation.

Authors' contributions

All authors contributed equally to the research design, data collection, analysis, and manuscript preparation, ensuring a collaborative and comprehensive approach to the study."

Conflicts of Interests

There is no conflict of interest.

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