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GASTROINTESTINAL STROMAL TUMOUR – EXPERIENCE OF A PERIPHERAL TERTIARY CARE INSTITUTE

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ABSTRACT **Introduction-** GIST is a generally a rare tumour but it is most common mesenchymal malignancy of gastrointestinal tract . this malignancy originates from the interstitial cells of Cajal, the pacemakers of GI tract. Management of GIST is associated with difficulties at diagnosis, proper immunohistochemical categorisation, completeness surgical excision,resistance to available TKIs. **AIMS -**Aim of this study was to share the experience of treating GIST cases from a peripherally located tertiary level hospital . **Methods-** In this retrospective observational study all the histology and immunohistochemistry proved cases of GIST attending Department of Radiotherapy of Midnapore Medical College between 2016 to 2017 were accrued and evaluated. **Result -** 12 Cases were evaluated for their demographic character, clinical presentation , treatment history, response pattern. M:F ratio was 1.4:1.Age range was 37 years to 58 years. Eleven cases were postoperative and 1 case was advanced inoperable. All the cases were positive for KIT stains .All the patients received treatment with Tyrosine Kinase inhibitor Imatinib Mesylate. At the end of 2 yrs of treatment and follow up 10 patients were disease free , two patients developed progression of disease. **Conclusion -** Introduction of Imatinib Mesylate and other TKIs have revolutionised the management of GISTs. Still the management is associated different obstacles like early diagnosis, proper immunohistochemical and genotypic categorisation, resistance to available TKIs , lack of large scale studies . Further long term studies with larger study population is needed to improve the treatment outcome of patients suffering from this mysterious disease.

KEYWORDS : GISTs, KIT, Tyrosine kinase inhibitors, Imatinib Mesylate

INTRODUCTION

GISTs are the commonest mesenchymal tumor arising from gastrointestinal tract although the overall incidence is less than 1% for the site. Incidence of GISTs is as documented in previous reports is from 0,43 to 2.2 per 100000 population.[1] Reports that examined stomach specimens from autopsy and surgery for other diseases suggests that there may be occult GISTs . it is often difficult to distinguish between benign and malignant GISTs . Retrospective studies have shown the presence of small GISTs (max. 10 mm) in 20% of individuals mostly in the proximal stomach and gastro oesophageal junction and less frequently in small and large bowel.[2] Most of the micro GISTs tend to regress or do not progress to clinical GISTs. Most of the GISTs develop as the result of activating mutations in KIT and PDGFRA genes encoding receptor protein tyrosine kinases[4]. Remarkable advances have been made in our knowledge of GISTs and development of molecular targeted therapies and tyrosine kinase inhibitors such as Imatinib or Sunitinib has dramatically changed the management and prognosis of patients with GISTs.Surgery is the treatment of choice and the only curative treatment for resectable GISTs.[4] But recurrence is very common particularly in patients with intermediate and high risk GISTs.TKIs have shown significant efficacy in many land mark trials in neoadjuvant , adjuvant and metastatic GISTs. There are many challenges associated with management of GISTs like a) difficulty in proper diagnosis based on histopathology , immunohistochemistry and genotyping , b) difficulty in achieving R0 resection , c) management of primary and secondary resistance to TKIs. In this study we have tried to report our institutional with experience of treating GIST cases in adjuvant and neoadjuvant setting with limited resources.

MATERIALS & METHODS

In this retrospective observational study was conducted at Department of Radiotherapy , of Midnapore Medical college which is a peripherally located tertiary care hoapital. All the histology and immunohistochemistry proved cases of GISTs attending the OPD in between 2016 to 2017 were accrued in this study. Information were collected after going through the individual patient record keeping files. Demographic features, clinical presentations, details of surgical treatment, histology and immunohistochemistry characteristics, history of treatment with Tyrosine kinase inhibitors , outcome after one year was recorded and tabulated.

After proper history taking all the cases were examined clinically.CECT scan of thorax and whole abdomen or pelvis was done as a part of metastatic work up. other investigations complete haemogram, liver function test, renal function tests were included in routine work up of all the patients. Details of the tumour characteristics (eg. location , size) detail of surgical management , type of surgery, gross description of the tumour were noted. Details histopathological features specially mitotic count was noted. Immunohistochemical staining was done in all the cases,specially to identify sensitivity to KIT or CD-117 , DOG-1 etc. all the cases positive for KIT stain in immunohistochemistry and having intermediate and high risk of relapse following complete R) resection were treated with Tyrosine kinase inhibitors like Imatinib Mesylate (400mg). During follow up patients were examined at monthly interval for first 6 months and thereafter at 3 monthly interval.complete haemogram, liver function tests, renal function tests, CECT scan of thorax and whole abdomen and pelvis , upper GI endoscopy were done during follow up period. All the observations were noted for 2 years of follow up period. All data was tabulated in excel sheet. Calculations were done using percentage and proportion method.

RESULTS

In the selected study population during the specified study period total 12 cases of histology and immunohistochemistry proved cases of GIST were identified. This was 2% of total number of cancer cases attending the Radiotherapy OPD for that time period. among them 7 cases were male(58.3%) and 5 cases were female (41.6%).Male : Female ratio was 1.4:1.maximum age noted was 58years and minimum age noted was 37 years.Mean age was 46 years. Eleven cases were postoperative, sent for adjuvant treatment.one case was advanced, inoperable and metastatic , sent for palliative treatment. Site wise distribution was as follows- Stomach (44%), Mesentry (33%), Jejunum (22%), Rectum(0.8%) . Clinical presentation were – Pain abdomen (66%), Vomiting(33%), , Lump in abdomen (25%), Melena (25%). Total 11 patients underwent exploratory laparotomy and resection or resection with anastomosis as primary modality of treatment. Maximum dimension of tumour noted was 13cm / 10cm. Minimum tumour size noted was 4cm/5cm. Among 11 postoperative cases only one case was found to have margin positive for malignant cells. Mitotic count in 2 cases were < 5(16%), another 2 cases between 6-10 (16%)and in 7 cases >10((58%). Risk categorisation of all the cases were done following NIH guideline considering the size of tumour and mitotic count. Among the 12 cases 2 cases were classified as low risk(16%), 2 cases intermediate risk(16%) and 7 cases high risk(58%) . Immunohistochemistry was done in all the cases. All the 12 cases were positive for CD-117 (100%). DOG1 marker was positive in 7 cases (58%). Nine patients were advised adjuvant treatment with Tyrosine kinase (Imatinib Mesylate) at a dose of 400 mg daily.One patient received Imatinib (400mg daily) for palliative purpose. All the patients were followed up at Radiotherapy OPD at one month interval for first 6 months and thereafter at 3 months interval . Follow up data of all the cases were evaluated for 2 years.At the end of 2 years , 10 cases were evaluable. One patient expired during follow up and one discontinued the treatment. Among 10 evaluable patients 8 were continuing treatment with Imatinib. One patient developed disease progression with Imatinib and was advised higher dose of Imatinib (800mg). Total 9 patients were disease free at the end of 2 years follow up. 7 patients on adjuvant Imatinib were disease free after 2 years of

treatment. All the patients tolerated Imatinib treatment fairly. No significant toxicities related to Imatinib treatment were noted other than diarrhoea, nausea , fatigue. Toxicities did not cause discontinuation of treatment and were managed conservatively.

DISCUSSION

GISTs are the most common mesenchymal tumour of GI tract, even though they account for less than 1% of all primary neoplasm of that site[1].The origin is postulated to be from interstitial cells of Cajal , the pacemaker cells of GI tract. Real incidence of GISTs could be much higher Retrospective studies have shown that presence of small GISTs (max-10 mm) is found in 20% of individuals . these are commonly found in proximal stomach and gastro oesophageal junction. Less frequently they are found in small and large bowel. [4,7]There are many challenges associated with determining the true incidence, this disease entity is relatively new based on immunohistochemical characterization with tyrosine kinase receptor expression reported in 1998. In an attempt to reclassify tumours formerly diagnosed as leiomyomas, leiomyosarcomas, schwannomas and rhabdomyosarcoma into GISTs by re evaluating the pathological specimens. GISTs most commonly occurs in stomach (60%), and Iieo jejunum (30%)followed by duodenum (5%), colorectum (4%) and rarely in appendix and oesophagus. In this study also the commonest site identified was stomach. Extra gastrointestinal GISTs are found outside GI tract eg- mesentry, omentum , retroperitoneum, liver, gallbladder, pancreas, vaginal septum pleura etc.[5] In Asian countries where gastric cancer is frequent GISTs may be more likely found incidentally during examination of surgical specimen than the areas where stomach cancer is less common. According to hospital based cancer registry majority of GISTs occur in 60 to 70 years of age . although in our study maximum and minimum age was 58years and 37 years respectively. Some cases are also found in paediatric age group[7].literature reports that they are usually part of syndrome such as Carney stratakis syndrome.85% of paediatric GISTs lack in KIT and PDGFRA mutation and most are succinate dehydrogenase deficient.[6]

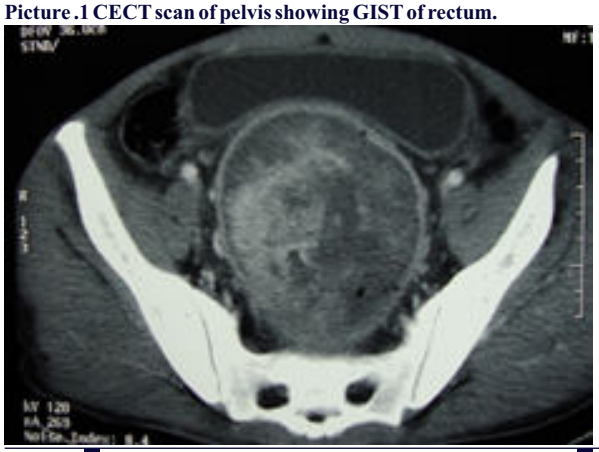
The symptoms associated with GISTs are abdominal pain, dysphagia, early satiety, less commonly there are anaemia, GI haemorrhage[6]. Approximately 70% cases are symptomatic, 20% are asymptomatic and identified during investigation and follow up for other malignancies. other 10% of cases are discovered during autopsy.[6]The size of GISTs varies from 1to 40 cm. In the present study maximum and minimum tumour size noted were 14 cm and 4 cm respectively. microscopically they are composed mostly of spindle cells (70%), epitheloid cells (20%) or mixed pathology. small bowel GISTs may contain eosinophilic aggregates of extracellular collagen. Diagnosis of GISTs is supported by immunohistochemical staining for KIT (CD-117) and /or DOG1. In case of negative results for both markers diagnostic confirmation should be sought by mutational analysis of KIT and PDGFRA genes. Approximately 85%- 95% of GISTs stain positive for KIT.[8] In the present study also all the cases were found to be KIT positive. But it has to be considered that other malignancies can also be positive for KIT , such as Melanoma, Angiosarcoma, Ewing Sarcoma, Seminoma and Small cell lung cancer.[8] The immunophenotypic profile should therefore be studied with morphological and clinical background. Recently a new antibody , DOG1 was identified which is a protein of chloride channel. It appears to be more sensitive than KIT regardless of the mutation status. A recent study evaluated 1168 cases of GISTs with different sites and histological subtypes which showed almost identical sensitivity of DOG 1 and KIT. But DOG 1 was more sensitive for epitheloid gastric GISTs and KIT is more sensitive in intestinal GISTs. Negative results for both the antibodies were observed in 2.6% cases.[9] However when used in combination with KIT it is an excellent biomarker for identification of GISTs. In the Consensus Conference held at the NIH in 2001 GISTs were stratified by risk category according to mitotic index (cut off 5/50 and 10/50).and tumour size (cut off 2 cm and 5 cm)[9]. Air Force Institute of Pathology (AFIP) is another risk categorisation system. Recent studies have added the site of tumour to the existing parameters which shows that gastric GISTs are associated with better prognosis than Intestinal GISTs. Tumour rupture (spontaneous or surgical) is also a negative prognostic factor due to peritoneal contamination. Metastases are generally to liver and peritoneum.[10] Rarely it can metastasize to skin, subcutaneous tissue, soft tissue, bone, lung, lymph nodes and bone marrow. It is important to discriminate between metastatic GISTs and multiple sporadic GISTs in a single patient.in the latter event different mutations are identified in different neoplasm for the synchronous lesion.[10] Over the past 2 decades, remarkable advances have been made in our understanding of GISTs and the development of molecular-targeted therapies, and tyrosine kinase inhibitors (TKIs) such as imatinib and sunitinib have dramatically changed the management and prognosis of patients with this malignancy. Although surgery is the treatment of choice and the only curative treatment for resectable GISTs, recurrence is common, particularly in patients with intermediate- and high-risk GISTs as defined by Miettinen and Lasota. landmark clinical trials demonstrating remarkable response of imatinib and sunitinib in patients with advanced unresectable and metastatic GIST, there arose great interest in evaluating the safety and efficacy of using TKI therapy in the adjuvant and neoadjuvant settings for patients with resectable intermediate- and high-risk, locally advanced, or limited resectable metastatic disease. The American College of Surgeons Oncology Group (ACOSOG) performed the first trials of imatinib in the adjuvant setting. ACOSOG Z90005 was a multicenter, single-arm, phase II study that enrolled 106 patients between September 2001 and September 2003, from 48 institutions, who underwent macroscopically complete resection of high-risk KIT-positive GISTs, defined as tumors C 10 cm, those with intraperitoneal tumour rupture or those with up to four peritoneal implants.[12,13] The results of this study showed that postoperative imatinib for 1 year prolonged recurrence-free survival (RFS) after complete GIST resection and was also associated with improved OS compared with historic controls (3-year OS 97%, 5-year OS 83% vs. historic 5-year OS 35%). The Scandinavian/German SSG XVIII/AIO trial8–12 was a randomized, open-label trial of 1 versus 3 years of postoperative imatinib (400 mg/day) after complete gross resection of high-risk KIT-positive GISTs following complete macroscopic resection . High-risk GIST was defined as tumours with at least one of the following: tumour diameter [10 cm, mitotic count [10/50 high-power fields (HPF), tumour diameter [5 cm and mitotic count [5/50 HPFs, or tumour rupture before or at the time of surgical resection. This study established a new standard for treating patients after resection of high-risk GISTs with adjuvant imatinib for 3 years. [14]The long-term data confirmed sustained OS benefit in the 3-year adjuvant imatinib arm.[14] The European Organization for Research and Treatment of Cancer (EORTC) conducted the randomized, open-label, phase III EORTC 62024 trial13 to compare 2-year adjuvant treatment with imatinib versus observation alone in patients with intermediate- and high-risk primary KITpositive GISTs. This study again supported the role of adjuvant imatinib in decreasing recurrence risk for patients with intermediate- and high-risk GISTs following complete macroscopic resection.[15] PERSIST-5 is a prospective, multicentre, single-arm, phase II study to evaluate whether adjuvant treatment with imatinib (400 mg/day) for 5 years is tolerable and efficacious. Eligible patients included those with a primary GIST of any location >/= 2 cm with .>/= 5 mitoses/50 HPFs, or primary non-gastric GIST >/=5 cm. Ninety-one patients from 21 institutions were enrolled, with data collected from 5 August 2009 through 20 December 2016. Primary and secondary endpoints included 5-year RFS and OS, respectively. Adjuvant therapy with imatinib for 5 years was demonstrated to be safe and effective at controlling recurrence rates in patients with imatinib-sensitive mutations.[16] However, compliance with this adjuvant regimen was challenging, with 49% of patients discontinuing therapy early. Neoadjuvant therapy is an attractive treatment strategy to downstage disease, allow definitive resection, and improve local disease control in patients with locally advanced and/or marginally resectable solid tumors across histologies for whom upfront surgery may be technically challenging, overly morbid, or not feasible. The Radiation Therapy Oncology Group (RTOG) 01321 was a prospective, multicentre, non-randomized, phase II trial evaluating the efficacy and tolerability of preoperative imatinib in patients with KIT-positive resectable intermediate- to high-risk primary (>5 cm) or recurrent/ metastatic (> 2 cm) GISTs. [17]Initial results of RTOG 0132/American College of Radiology Imaging Network (ACRIN) 6665 were reported in 2008 and demonstrated that preoperative imatinib for 8–12 weeks was safe and well tolerated. Although survival outcomes at 2 years compared favourably with historical single-institution surgical series for patients with intermediate- to high-risk GISTs, it was unclear whether the apparent survival benefits seen in this study could be attributed to the use of imatinib preoperatively, or due to the 2 years of postoperative imatinib therapy. [17]In the pre-imatinib era, surgical resection of recurrent and metastatic GISTs was associated with improved survival if complete gross resection could be achieved. However, complete resection was often difficult to achieve due to the multifocal nature of recurrent and metastatic GISTs. In the post-imatinib era, TKI therapy is the standard first-line treatment for patients with metastatic, recurrent, and/or inoperable GISTs. Maximal response to imatinib is typically achieved within 6–18 months of

treatment,22 complete remissions are rare and median time to recurrence/ progression on imatinib is within 2 years. Most inoperable or metastatic GISTs show a clinical response to imatinib which can be verified with the appropriate radiological exams. A portion remain stable while a minority progress in the first six months ie, primary resistance. Secondary resistance occurs when the disease progresses after an initial response (generally after 12-36 months) . These mutations are often located in exons 13, 14 and 17 . The primary mutation in resistant patients is still sensitive to pharmacologic treatment. In the case of disease progression, the pharmacologic option is to increase the dose of imatinib (600- 800 mg). Alternatively, sunitinib may be administered as second-line therapy after the failure of imatinib .In addition to acting as a KIT and PDGFRA inhibitor, sunitinib also acts as antiangiogenic factor, and has demonstrated efficacy against secondary mutations located in exons 13 and 14. Sunitinib may also be considered as first-line therapy in cases with mutation in exon 9 or wild-type (including paediatric cases). Other drugs may be considered in patients resistant to both imatinib and Sunitinib , including Sorafenib , Nilotinib or Dasatinib . Overall, around 50% of patients with localized GIST do relapse. The median time to recurrence averages around two years, with variations which of course depend on the biology of the tumour. Recurrences typically affect the abdomen (extra-abdominal metastases, such as bone lesions, tend to be rare and/or late events).[19] Even when radiologic findings suggest a single lesion, the treatment of choice is currently medical therapy with imatinib. Cytoreductive surgery for recurrent or metastatic GISTs may be considered in select circumstances, including in patients presenting with oncologic emergencies such as haemorrhage, intestinal perforation, or obstruction, as well as in patients whose disease is stable or responsive to TKI therapy and when complete gross resection is possible and in patients with limited disease progression. Currently available data do not support a clinical benefit of surgery for patients with generalized disease progression on TKI therapy. Raut et al. reported that 1-year PFS following surgical resection was 80%, 33% and 0% in patients with advanced GIST who achieved SD, limited progression, and generalized progression, respectively, with imatinib therapy preoperatively.[18]

CONCLUSION

GIST is a rare cancer that has several challenges compared with more common cancers. Generally, physicians may have little experience and knowledge about it because of its rarity. Consequently, such patients show poorer prognosis than those with more common cancer. Awareness, high level of clinical suspicion, thorough histological, immunohistochemistry , mutational analysis are essential for better management of GIST cases. Multidisciplinary team approach is very much needed for successful management of this malignancy. The development of TKIs has dramatically altered the management landscape and improved outcomes of patients with GISTs. Initially limited to use in the metastatic setting, TKIs have since been shown to have utility both in the neoadjuvant and adjuvant settings. The rationale use of TKI therapy in the metastatic, neoadjuvant, and adjuvant settings requires knowledge of GIST mutational status, obtained through tumour biopsies prior to initiation of systemic therapy . Imatinib and subsequent generations of TKIs have to date primarily benefitted patients with GISTs harbouring common KIT mutations. Further studies are required to ascertain the role of newer therapies along with surgical management for growing subsets of patients of GISTs.

Picture .1 CECT scan of pelvis showing GIST of rectum.



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