MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.59218/makrjms.2023.10.10.17

Evaluation of Medical and Surgical Management of Gastrointestinal Stromal Tumors: A Retrospective Analysis

[1]J.N. Malleswara Rao, [2]K. Punyavathi Poojitha, [3]Syam Kumar Addepalli and [4]Mohan Patro

[1,4]Department of General Surgery, GITAM Institute of Medical Sciences and Research, Visakhapatnam Andhra Pradesh, India

[2,3]Department of Pharmacology, GITAM Institute of Medical Sciences and Research, Visakhapatnam Andhra Pradesh, India

OPEN ACCESS

Key Words
GIST, Immunohistochemistry study, Molecular genetic study, Imatinib

Corresponding Author
Mohan Patro,
General Surgery, GITAM Institute of Medical Sciences and Research, Visakhapatnam. Andhra Pradesh, India
drmohanpatro@gmail.com

Author Designation
[1]Assistant Professor
[2,3]Associate Professor
[4]Former Professor and Head

Received: 18 August 2023
Accepted: 26 September 2023
Published: 8 October 2023

Citation: J.N. Malleswara Rao, K. Punyavathi Poojitha, Syam Kumar Addepalli and Mohan Patro, 2023. Evaluation of Medical and Surgical Management of Gastrointestinal Stromal Tumors: A Retrospective Analysis. Res. J. Med. Sci., 17: 10-17, doi: 10.59218/makrjms.2023.10.10.17

ABSTRACT
Gastrointestinal stromal tumors (GIST) are mesenchymal tumors that arise from interstitial cells of Cajal in the gastrointestinal tract (GIT). They constitute about 0.2% of all gastrointestinal tumors. Even though effective chemotherapy has been developed, surgery remains the standard treatment for resectable tumors. GIST are rare GIT tumors. The main purpose is to evaluate various methods of management of GIST from our hospital. This manuscript aims to create awareness among General Surgeons regarding the workup and management of GIST in clinical practice. This is a retrospective analysis conducted in GIMSR, Visakhapatnam. All the cases diagnosed as GIST and managed in our institute from 1st February 2021 to January 30, 2023, were included in the study. After the clinical examination, the patients underwent endoscopy and imaging studies like the ultrasound Scan of the abdomen, CECT (Contrast Enhanced Computed Tomography) of the abdomen and immuno-histo-chemistry (IHC) studies. All patients who were diagnosed with the disease were subjected to excisional surgery as the primary modality of treatment except for the inoperable cases. Seven cases of GIST were managed in this study. Tumors were seen to arise from the stomach (4/7), ileum (2/7) and omentum (1/7). "The surgical management of these seven cases after complete workup included: resection and anastomosis of two cases of ileal tumors, wedge resection with adequate margin in two cases of stomach tumors, sleeve resection of the stomach in one case and omentectomy in one case along with the resection of the tumor had been done after investigations." Chemotherapy was given to all deserving cases. GIST patients need CECT for accurate localization and operability. Immunohistochemistry study and Molecular genetic study should be done in all cases. Management of cases depends on site, size, operability, mitotic count and immunohistochemistry results. Each patient's management should be individualized. CD117-positive cases show a good response to chemotherapy. Follow-up should be done once in six months.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are histologically heterogeneous groups of mesenchymal tumors that arise from interstitial cells of Cajal, the pacemaker cells in the gastrointestinal tract (GIT). Even though they represent only 0.2% of all GI tumors, they are the most common sarcomas of GIT. These tumors are mostly seen in the stomach and small bowel[1]. These tumors are also called smooth muscle tumors of uncertain malignant potential (STUMP) and Smooth Muscle origin gastrointestinal autonomic nervous tumors (GANT) because of the similarity of their cells to neural cells in the autonomic myenteric plexus. They are typically defined as tumors whose behavior is driven by mutations in the Kit gene or PDGFRA gene and may or may not stain positively for Kit[2]. Though GIST occurrence is rare, all general surgeons must be aware of the management of these tumors.

Based on immuno-histochemical studies the GIST are classified into four prototypes: Myoid, Neural, Dual differentiation and Indeterminate types. The immunohistochemical expression of CD-117 (a growth factor receptor with tyrosine kinase activity) is the most important defining feature of GIST since a spindle-shaped tumor in the GIT with CD-117 positivity is virtually diagnostic of GIST. CD-117 is present in all GIST but not in true smooth muscle and neural tumors. Positivity for CD-34 is also common and occurs in 60-80% of GIST. Other antigens like Vimentin, Nestin 90-100% positivity, Desmin, Neuron-specific enolase, Neurofilament and Smooth muscle actin (SMA) might be expressed by some of these tumors. Preoperative diagnosis may remain difficult and is not essential in all cases. The SMA expression showed the opposite patterns and was most frequent in the GIST of the small bowel (47%) and rarest in the GIST of the rectum and esophagus (10-13%)[3].

A wide variety of mesenchymal tumors in the GIT or abdominal cavity can partially overlap with GIST in their gross characteristics, histology and immunophenotype type. The differential diagnosis of GIST would include smooth muscle tumors (leiomyomas and leiomyosarcomas), schwannomas, fibromatoses and high-grade sarcomas[2]. GIST now is the most common mesenchymal tumor of the GIT which has been frequently studied, especially concerning its successful surgical and targeted therapy using Imatinib mesylate[4].

Aim: To evaluate the medical and surgical management of gastrointestinal stromal tumors at a tertiary care hospital.

MATERIALS AND METHODS

This is a retrospective analysis done in the Department of General Surgery, GITAM Institute of Medical Sciences and Research, GITAM Deemed to be University, Visakhapatnam. The study period is two years, from 1st February 2021 to January 30, 2023. The study population includes patients who were diagnosed with GIST after necessary investigations. All the cases diagnosed with GIST managed in our institute during the study period were included in the study. After the clinical examination, the patients underwent endoscopy with biopsy, immuno-histo-chemistry studies and imaging studies like US Scan of the abdomen and CECT (Contrast Enhanced Computed Tomography) of the abdomen.

Preoperative necessary investigations were done in all the cases before they underwent surgery as the primary modality of treatment. The investigations include complete blood counts, fasting blood glucose, renal function tests and liver function tests. Chest X-ray, ECG and Echocardiogram were done for patients over 40 years and those suffering from co-morbid conditions. Those patients suffering from co-morbid conditions were treated adequately by the respective Physicians and then taken up for surgery. The pre-anesthetic assessment was done in all the cases. Each patient and their close relatives were explained about the procedure and possible complications that can be encountered during surgery and written informed consent was taken.

The resected specimens were fixed in formalin and embedded in paraffin. The specimens were cut into 4-micro mm sections and were used for staining with hematoxylin and eosin and for immunohistochemistry. Several IHC stainings were used including desmin, alpha-SMA, S-100 protein, CD 34, CD 117 and vimentin.

RESULTS

Gastrointestinal stromal tumors were diagnosed in seven patients during the study period and all of them were managed at our institute. Gender distribution was 5 males and 2 females and the ages of the patients varied from 30-64 years with a mean age at presentation of 47.1 years.

All seven patients presented with dull aching abdominal pain of various magnitude, mostly in the upper and central abdomen. The duration of the illness varied from 3 months to 9 months. Only two patients presented with bleeding and anemia. On examination, five patients were of average build and two were thin-built. Abdominal examination revealed a palpable mass in the upper abdomen in three cases of gastric GIST. Omental GIST and one of the small intestine GIST are also presented with a palpable mass in the central abdomen.

The results from upper gastrointestinal endoscopy showed evidence of tumors in the stomach in four cases. There was rounded tumor mass in two cases; of which one was in the fundus and the other was in the body. Both were between 3-5 cm in size. One tumor was very extensive and it was suspected of carcinoma

of the stomach. The other tumor was also less than 5cm in size. A biopsy was taken from all the tumors. However, only two cases had features of GIST from the biopsy.

The results from the ultrasound scan of the abdomen did not reveal any ascites or any secondaries in the liver in any case.

Contrast enhanced computed tomography (CECT) demonstrated tumors in all the cases and gave information about the size, site, shape, relationship and infiltration of tumors.

Chest X-ray did not reveal any abnormality in any case. There was no evidence of secondary metastasis in the lungs either.

All patients were subjected to excisional surgery as the primary modality of treatment except in one inoperable case. Patients of the high-risk group and those positive for CD117 were offered postoperative chemotherapy as per the guidelines of NCCN, mainly Imatinib mesylate[5]. Patients were kept on regular follow-up at 6 monthly intervals with clinical examination and US Scan of the abdomen (Table 1). NCCN (National Comprehensive Cancer Network) 2003 and 2009 and (Version 6.2019 February 10, 2020); has developed an integrated suite of tools to improve the quality of cancer care.

Tumors were seen to arise from the stomach (4/7), ileum (2/7) and omentum (1/7). Resection of ileal tumors with adequate margin and anastomosis was done in two cases. Wedge resection of stomach tumors with adequate margin was done in two cases and sleeve resection of the stomach along with tumor was performed in one case. Omentectomy along with the tumor was carried out in one case. On the table, it was found that one case of gastric GIST was not resectable because of extensive infiltration. Hence the patient was put on Imatinib Mesylate. All operated cases had uneventful recovery.

On exploration, two of the gastric tumors were nearly 3cms in diameter, firm in consistency and sessile. Wedge resection of the tumors with adequate margin was done. One of the gastric tumors was present on the greater curvature around 4.5 cm in size and firm in consistency. A sleeve resection of the stomach was performed along with the tumor. In one of the patients with gastric tumors, there was a huge lesion that was infiltrating the surrounding tissues. It was not resectable. The omental tumor was nearly 7.5 cm with smaller nodules nearby with omental adhesion. The tumor was resected along with an adequate margin of omentum. One jejunal tumor was 2.5cms and firm but intraluminal. The tumor was resected with adequate margin and end-to-end anastomosis was performed. In one patient tumor was arising from the proximal ileum, nearly 6.5cm, firm and extraluminal. Resection of the ileal segment with the tumor was done and continuity was obtained by end-to-end anastomosis.

Tumor size was more than 5 cm in three cases and 3-5 cm in four cases. Mitotic count: Six cases had 6-10/50 high power field (HPF) and one case had >10/50 HPF. Post-operative chemotherapy with Tyrosine kinase inhibitor Imatinib Mesylate was given at the dose of 400 mg daily in all cases.

Histopathological examination revealed sheets with high cellularity containing large epithelioid cells and spindle-shaped cells with increased cellularity and mitoses and a diagnosis of intermediate-type malignant GIST was made in four cases and high-grade type in three cases (Fig. 1).

The immunohistochemical study of the tumor revealed positivity for CD 117 (c-kit) in all cases by showing the reaction with tumor cells (Fig. 2), tumor cells also showed positive staining for CD 34 in four cases (Fig. 3) and reaction for Vimentin was found in five cases. The resected margins of the specimens were

Table:1: Illustrates the information about the patient

Patient information	Stomach GIST		Ileal GIST		Omentum GIST	
Age 30-64 years	4 (57.15%)		2 (28.56%)		1 (14.28%)	
Sex						
Male: 5 (71.42%)	3 (42.86%)		1 (14.28%)		1 (14.28%)	
Female: 2 (28.58%)	1 (14.29%)		1 (14.28%)		0	
Presentation						
Abdominal lump	2 (28.57%)		1 (14.29%)		1 (14.29%)	
Dull aching pain in abdomen	4 (57.13%)		2 (28.58%)		1 (14.29%)	
Bleeding	2 (28.58%)		0		0	
Anemia	2 (28.58%)		0		0	
Investigations	>10	>9	>10	>9	>10	>9
Hemoglobin (g dL^{-1})	3(42%)	1(14%)	1(14%)	1(14%)	1(14%)	
US Scan of the abdomen (+ve)	3 (42%)		1 (14%)		1 (14%)	
CECT (+ve)	4 (57%)		2 (28%)		1 (14%)	
Endoscopy and biopsy (+ve)	2 (28%)		0		0	
Chest X-Ray	0		0		0	
Immunohistochemistry						
CD 117: 7 cases (100%)	4 (57.14%)		2 (28.57%)		1 (14.28%)	
CD 34: 4 cases (57.14%)	3 (42.85%)		1 (14.28%)		0	
Vimentin: 5 cases (71.42%)	3 (42.85%)		1 (14.28%)	1	(14.28%)	

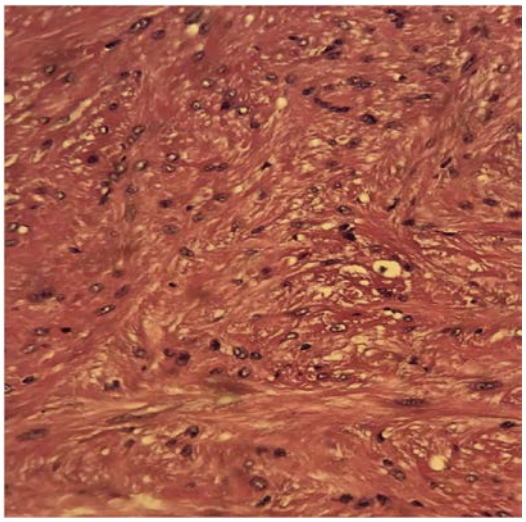

Fig. 1: Histopathological features are suggestive of low-grade GIST

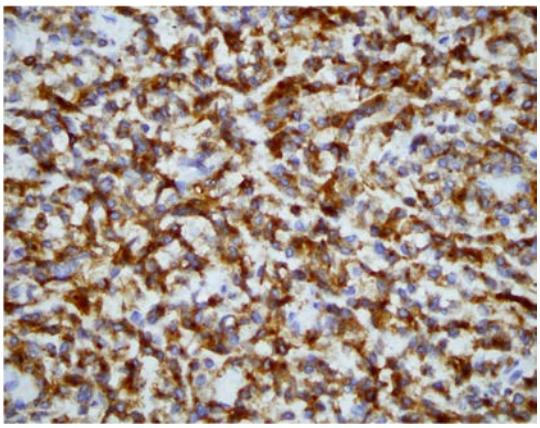

Fig. 2: Tumour cells showing CD117 positivity

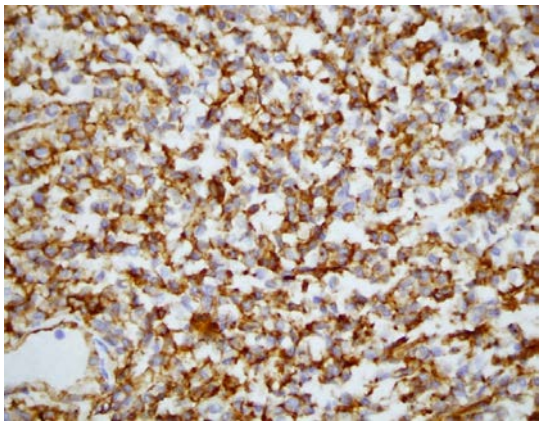

Fig. 3: Tumor cells showing CD34 positivity

free from tumors. Tumor markers and molecular genetic studies were conducted, ensuring comprehensive treatment and assessment (Fig. 4-8).

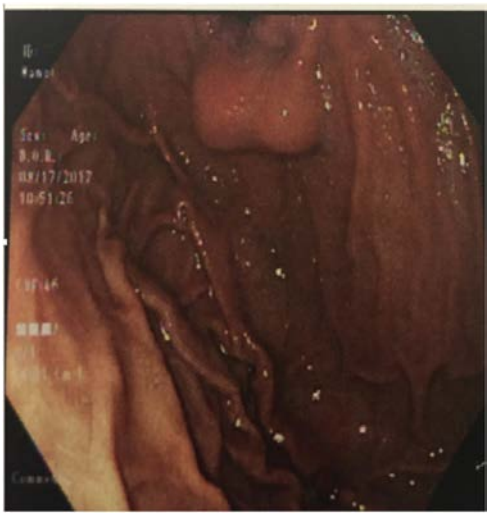

Fig. 4: UGI Endoscopy shows oval solid mass arising from the fundus of the stomach suggestive of Fundic GIST

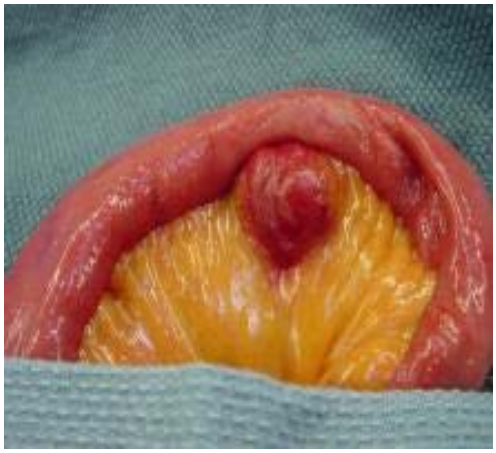

Fig. 5: On table showing sessile rounded mass arising close to the mesenteric border of small bowel

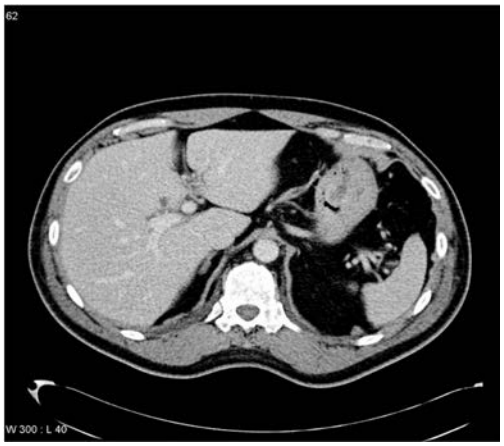

Fig. 6: CECT showing a large lesion with homogeneous enhancement located in the stomach, suggestive of GIST of the stomach

Table 2: Illustrates the location of tumor, tumor size, mitotic count, grading of tumor, operative procedure and prognosis of the patient

Patient information	Stomach GIST No. (%)	Ileal GIST No. (%)	Omental GIST No. (%)
Location of Tumor	4 (57.14)	2 (28.57)	1(14.28)
Tumor size	>5 cm: 1 (14.2) 3-5 cm: 3 (42.85)	>5 cm: 1 (14.2) 3-5 cm: 1 (14.2)	>5 cm: 1 (14.2) 3-5 cm: 0 (0)
Mitotic count	6-10: 4 (57.1) >10: 0 (0)	6-10: 1 (14.2) >10: 1 (14.2)	6-10: 0 (0) >10: 1 (14.2)
Grading of Tumor	HG: 1 (14.2); IG: 3 (42.85)	HG: 1 (14.2); IG: 1 (14.2)	HG: 1 (14.2); IG: 0
Operative Procedures	WE: 2 (28.5); S: 1 (14.2); IO: (14.2)	R and A: 2 (28.5)	OT: 1 (14.2)
Prognosis	LTF: 1 (14.2); Well: 2 (28.57); Died: 1(14.2)	Well: 2 (28.57)	Well: 1 (14.2)

HG: High grade, IG: Intermediate grade, WE: Wide excision, SR: Sleeve resection, IO: Inoperable, R and A: Resection and anastomosis, OT: Omentectomy with tumor and LTF: Lost to follow-up

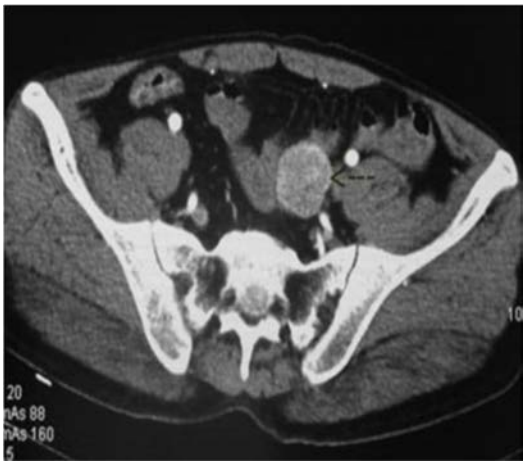

Fig. 7: CECT showing well-defined heterogeneous lesion in the small intestine suggestive of GIST

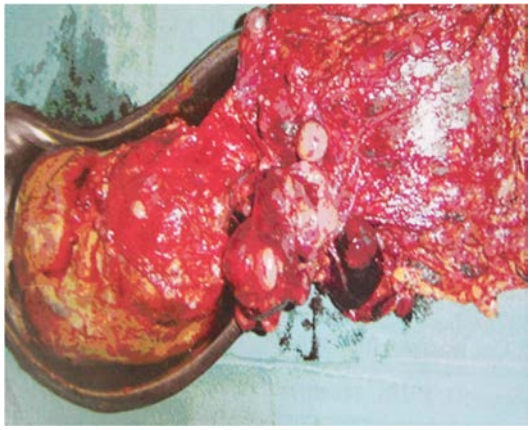

Fig. 8: Resected specimen showing the solid tumor mass in the omentum suggestive of Omental GIST

Follow-up was carried out at 6 monthly intervals by clinical assessment, Ultrasound scan of the abdomen and CECT scan in doubtful recurrence cases.

Prognosis: One patient with unresectable gastric GIST was put on Imatinib mesylate but despite treatment, the patient died after six months of adequate treatment. One patient was lost to follow-up. No case had any distant metastasis or recurrence during the follow-up period (Table 2).

DISCUSSIONS

GIST arises from an indistinct multipotent cell line of origin. GIST are rare tumors, with an estimated incidence of 1.5/100 000/year which includes only the clinically relevant GIST. A much higher number of microscopic lesions could have been found pathologically[6]. GIST occurs predominantly in middle-aged or elderly, at a median age of 58 years. The majority of GIST which is around 60-70% have been reported to arise in the stomach, whereas 20-30% originate in the small intestine and less than 10% in the esophagus, colon and anorectal region. GIST also occurs in the extra-intestinal abdominopelvic sites such as the omentum, mesentery, or retroperitoneum. GIST are graded into 3 categories Low grade, Intermediate grade and High grade or risk[7].

Less frequently, GIST may arise in the appendix, gall bladder, pancreas, retroperitoneum, paravaginal and periprostatic tissues[8]. Approximately 20-25% of gastric GIST and 40 to 50% of small intestine GIST are clinically aggressive[2,9]. It has been estimated that approximately 10-25% of patients present with metastatic disease[8-10].

In a study conducted by Rubio *et al*.[11] the incidence of GIST was given as 50% in the stomach, 43.5% in the small intestine, 4.3% in the omentum and 2.2% in the colon. 37% were classified as high risk of aggressive behavior, 30.4% as intermediate risk and 32.6% as low or very low risk. Whereas, in our study 57.14% of lesions were in the stomach, 28.57% in the small intestine and 14.28% in the omentum. Intermediate-grade lesions were 57.14% and high-grade lesions were 42.85%.

A common presentation of GIST tumors varies according to the site and size of the tumor. Small tumors are often asymptomatic or detected incidentally. Whereas large tumors may present as abdominal pain, fullness of the abdomen, early satiety, loss of weight and mass abdomen. These tumors may ulcerate and/or bleed. Anemia may be predominant in cases of bleeding GIST. In our series 71.42% of patients presented with abdominal mass and all had dull aching abdominal pain; whereas 28.58% of cases presented with bleeding and anemia[7].

Endoscopic ultrasound with fine-needle aspiration biopsy is useful in the detection of GIST in the upper GI tract because most tumors arise below the mucosal

layer and grow in an endophytic fashion[12,13]. In our study, only two cases of Gastric GIST were diagnosed by endoscopic biopsy before operation.

A diagnosis of GIST is typically confirmed by immunohistochemical staining for c-KIT, also known as CD117 since approximately 95% of GISTs express c-KIT[1,14]. It is one of the most robust markers for GIST and, therefore, an essential analytical test[15]. In addition, 60-70% of GIST are positive for CD34, a transmembrane glycoprotein that is expressed by hematopoietic progenitor cells and a variety of other cells[1].

The immunohistochemical study of the tumor revealed positivity for CD 117 (c-kit) in all our cases (Fig. 6), CD 34 in four cases (Fig. 7) and Vimentin in five cases.

c-KIT-negative GIST may also be positive for two additional markers, DOG1 and protein kinase C-theta[14]. Therefore, genotyping may help confirm the diagnosis of a suspected KIT-negative GIST[16].

Multidisciplinary treatment planning is needed involving Pathologists, Radiologists, Surgeons and Medical Oncologists. Standard treatment of localized GIST is complete surgical excision, without dissection of clinically negative lymph nodes. R0 excision is the goal. If R0 surgery is not feasible, or it could be achieved through less mutilating surgery in the case of cytoreduction, imatinib pretreatment is recommended[6]. In our series six out of seven cases were operated according to the site and size of the lesion. A case of gastric GIST was inoperable.

The standard of care for managing patients with GIST has rapidly changed after the introduction of effective molecularly targeted therapies involving Tyrosine Kinase inhibitors. They block the activity of the tyrosine kinase product of C-Kit. Drugs such as Imatinib Mesylate and newer drug Sunitinib Malate are used in Imatinib refractory cases. A better understanding of the molecular characteristics of GIST has improved diagnostic accuracy and led to the discovery of novel immunomarkers[5].

Indications of chemotherapy are high-risk group, metastasis, unresectable or incompletely resected tumors and patients with CD117 positive. In our series 6 patients were given chemotherapy and 1 case was lost to follow up. Mutations in the exons 11,9 and rarely 13 and 17 of the c-kit gene are known to occur in GIST. A D816V point mutation in *c-kit* exon 17 is responsible for resistance to targeted therapy drugs like Imatinib Mesylate, a tyrosine kinase inhibitor. Mutations in *c-kit* and *PDGFrA* are mutually exclusive[2]. In locally advanced inoperable patients and metastatic patients, Imatinib is a standard lifelong treatment. This applies also to metastatic patients who have been completely relieved of all lesions surgically. The standard dose of Imatinib is 400 mg daily. Patients with exon 9 KIT mutations fare better in terms of progression-free survival on a higher dose level, i.e. 800 mg daily. Treatment should be continued indefinitely since treatment interruption is generally followed by relatively rapid tumor progression in virtually all cases, even when lesions have been previously surgically excised[6].

Most reliable prognostic factors are the size of the tumor, mitotic rate, location, specific histological subtypes, the degree of cellular pleomorphism, age of the patients, local invasion, resectability of tumors, metastasis can be used to predict the risk of recurrence in GIST patients. Tumors of <2 cm with a mitotic rate of <5/50 HPF have been shown to have a lower risk of recurrence than larger or more aggressive tumors. Nevertheless, all GIST tumors should be considered to have malignant potential. Small bowel tumors have higher malignant potential[7,17].

In general, secondary resistance occurs with sunitinib, often around 2-3 years, very similar to imatinib, requiring the next therapy. Took a little while to develop, with sunitinib approved in 2006 but regorafenib a single-agent was approved in 2013. It targets KIT and the PDGFR as well as a variety of other targets. This dosing was 160 mg day^{-1}, days 1 through 21 and then off for 7 days; following publication of data from the phase III GRID study[18]. Neoadjuvant treatment with these agents appears to stabilize disease in the majority of patients and may reduce the extent of surgical resection required for subsequent complete tumor removal[19].

Metabolic responses seen on positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (18FDG) are closely related to clinical benefit. Furthermore, these metabolic changes are preceded by weeks or months of a significant decrease in tumor size on computed tomography (CT). Conversely, lack of metabolic response on FDG-PET indicates primary resistance to the drug and may help identify patients who would benefit from another therapy, while re-emergence of metabolic activity within tumor sites following a period of therapeutic response indicates secondary resistance to the drug[20].

Adverse events with these drugs, included edema, fluid retention, elevated proteinuria, nausea, vomiting, diarrhea, fatigue, myalgias, skin rash, thinning of hair, change in color of the hair, dry mouth, bone marrow suppression, bleeding into the gastrointestinal tract or intratumoral bleeding and elevations in aspartate aminotransferase, alanine aminotransferase, or bilirubin. Hypertension is the most common cardiovascular toxicity that was seen with VEGF signaling pathway inhibitors, namely, sunitinib and regorafenib. Other cardiovascular risks include arterial and venous thromboembolism risk, left ventricular dysfunction and congestive heart failure. Another

common adverse effect of sunitinib and regorafenib is hand-foot skin reaction (HFSR). These are usually hyperkeratotic lesions or painful blisters that form in pressure points on the hands and feet[21]. Other dermatological side effects are general erythema or a maculopapular rash with seborrheic dermatitis. Sunitinib and regorafenib can result in hypothyroidism, so monitoring thyrotropin and thyroxine levels is important. Although rare, it has been seen in drug-induced hepatitis. It is also important to monitor the complete blood cell count owing to potential risks of neutropenia, anemia and thrombocytopenia[22,23]. In locally advanced inoperable patients and metastatic patients, Imatinib is the standard treatment[23,24].

There is also a role in early-stage disease for imatinib. In the neoadjuvant setting, it can be used to try to make a tumor resectable or to potentially decrease the extent of the surgery. There is controlled evidence that patients who have already progressed on imatinib may benefit when re-challenged with the same drug in metastatic or unresectable gastrointestinal stromal tumors[23,25].

Complete excision of residual metastatic disease is related to a good prognosis, provided the patient is responding to imatinib but it has never been demonstrated prospectively whether this is due to surgery or to patient selection[23,26,27].

CONCLUSION

All GIST patients need CECT for accurate localization and relationship of the tumor with surrounding structures. An immunohistochemistry study should be done in all cases. Management depends on the site, size of the tumor, operability, mitotic count and immunohistochemistry results and each patient's management should be individualized. Surgery is the primary treatment of choice in localized or potentially resectable GIST. Surgery and imatinib form the first-line therapy and their effectiveness for the majority of patients has been revolutionary. Sunitinib and Regorafenib are approved second-line agents that are effective in many non-responders to imatinib therapy. CD117 positive cases show a good response to Imatinib mesylate. Follow-up should be done once in six months. Personalizing the treatment of GISTs and tailoring treatments to tumor genotypes using combination therapies to prevent the emergence of resistance is essential to optimize patient outcomes.

REFERENCES

1. Fletcher, C.D.M., J.J. Berman, C. Corless, F. Gorstein and J. Lasota *et al*., 2002. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum. Pathol., 33: 459-465.
2. Miettinen, M. and J. Lasota, 2006. Gastrointestinal stromal tumors: Review on morphology, molecular pathology, prognosis and differential diagnosis. Arch. Pathol.Lab. Med., 130: 1466-1478.
3. Miettinen, M., L.H. Sobin and M. Sarlomo-Rikala, 2000. Immunohistochemical spectrum of GISTS at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod. Pathol., 13: 1134-1142.
4. Judson, I. and G. Demetri, 2007. Advances in the treatment of gastrointestinal stromal tumours. Ann. Oncol., 18: x20-x24.
5. Demetri, G.D., M. von Mehren, C.R. Antonescu, R.P. DeMatteo and K.N. Ganjoo *et al*., 2010. NCCN task force report: Update on the management of patients with gastrointestinal stromal tumors. J. Nat. Compr. Cancer Network, Vol. 8. 10.6004/jnccn.2010.0116
6. Casali, P.G. and J.Y. Blay, 2010. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol., 21: v98-v102.
7. Chandramohan, K., M. Agarwal, G. Gurjar, R.C. Gatti, M.H. Patel, P. Trivedi and K.C. Kothari, 2007. Gastrointestinal stromal tumour in Meckel's diverticulum. World J. Surg. Oncol., Vol. 5. 10.1186/1477-7819-5-50
8. Corless, C.L., J.A. Fletcher and M.C. Heinrich, 2004. Biology of gastrointestinal stromal tumors. J. Clin. Oncol., 22: 3813-3825.
9. Joensuu, H., 2006. Gastrointestinal stromal tumor (GIST). Ann. Oncol., 17: x280-x286.
10. DeMatteo, R.P., J.J. Lewis, D. Leung, S.S. Mudan, J.M. Woodruff and M.F. Brennan, 2000. Two hundred gastrointestinal stromal tumors. Ann. Surg., 231: 51-58.
11. Rubió, J., R. Marcos-Gragera, M.R. Ortiz, J. Miró and L. Vilardell *et al*., 2007. Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. Eur. J. Cancer, 43: 144-148.
12. Nickl, N.J., 2004. Gastrointestinal stromal tumors: New progress, new questions. Curr. Opin. Gastroenterol., 20: 482-487.
13. Hou, Y., A. Collinsworth, F. Hasa and L. Griffin, 2023. Incidence and impact of surgical site infections on length of stay and cost of care for patients undergoing open procedures. Surg. Open Sci., 11: 1-18.
14. Kindblom, L.G., H.E. Remotti, F. Aldenborg and J.M. Meis-Kindblom, 1998. Gastrointestinal pacemaker cell tumor (GIPACT): Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am. J. Pathol., 152: 1259-1269.
15. West, R.B., C.L. Corless, X. Chen, B.P. Rubin and S. Subramanian *et al*., 2004. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of kit or PDGFRA mutation status. Am. J. Pathol., 165: 107-113.

16. Medeiros, F., C.L. Corless, A. Duensing, J.L. Hornick and A.M. Oliveira *et al*., 2004. Kit-negative gastrointestinal stromal tumors: Proof of concept and therapeutic implications. Am. J. Surg. Pathol., 28: 889-894.
17. Raut, C.P. and R.P. DeMatteo, 2008. Evidence-guided surgical management of GIST: Beyond a simple case of benign and malignant. Ann. Surg. Oncol., 15: 1542-1543.
18. Demetri, G.D., P. Reichardt, Y.K. Kang, J.Y. Blay and P. Rutkowski *et al*., 2013. 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, 381: 295-302.
19. Rammohan, A., 2012. A gist of gastrointestinal stromal tumors: A review. World J. Gastrointestinal Oncol., 5: 102-112
20. den Abbeele, A.D.V., 2008. The lessons of GIST-PET and PET/CT: A new paradigm for imaging. Oncologist, 13: 8-13.
21. Kollmannsberger, C., G. Bjarnason, P. Burnett, P. Creel and M. Davis *et al*., 2011. Sunitinib in metastatic renal cell carcinoma: Recommendations for management of noncardiovascular toxicities. Oncologist, 16: 543-553.
22. Dagher, R., M. Cohen, G. Williams, M. Rothmann and J. Gobburu *et al*., 2002. Imatinib Mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin. Cancer Res., 8: 3034-3038.
23. ESMO., 2014. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Onchol., 25: III21-III26.
24. ESMO, 2012. Gastrointestinal stromal tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Onchol., 23: VII49-VII55.
25. Kang, Y.K., M.H. Ryu, C. Yoo, B.Y. Ryoo and H.J. Kim *et al*., 2013. 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., 14: 1175-1182.
26. Du, C.Y., Y. Zhou, C. Song, Y.P. Wang and Z.G. Jie *et al*., 2014. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: A prospective randomised trial in China. Eur. J. Cancer, 50: 1772-1778.
27. Shubhankar, G., R. Singh, M. Vats, A. Reddy and N. Solanki, 2020. Current management of gastrointestinal stromal tumor. MAMC J. Med. Sci., Vol. 6, No. 1. 10.4103/mamcjms. mamcjms_81_19