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Gastrointestinal Stromal Tumor: Review

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ABSTRACT

Gastrointestinal stromal tumours (GISTs) are one of the most common mesenchymal tumors affecting the gastrointestinal (GI) tract. GIST has undergone outstanding development in how they are presented, classified, assessed, diagnosed and treated over the last decade. Gastrointestinal stromal tumours (GIST) account for nearly less than 3% of all malignant GI tumours. The clinical presentation can differ depending on its location, tumour size and aggressiveness of the tumour. In this comprehensive review, we talk regarding the epidemiology, clinical features and diagnostic modalities for GIST. We also discuss our view regarding the treatment options for early stage, locally advanced and metastatic GIST. Indications for neoadjuvant and adjuvant therapy along with time of therapy are also explained. A concise discussion of most recent biomarkers is also provided.

Key Words: GIST, Leiomyoma, Leiomyosarcoma, Leiomyoblastoma, Stromal tumours, Mesenchymal neoplasm

1. INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a most common intestinal tumor of mesenchymal origin which is believed to be originated from the interstitial cell of Cajal. In 1983, Mazur and Clark coined the term GIST. In past, this mesenchymal tumor was identified as leiomyoma, leiomyoblastoma and leiomyosarcoma, the tumor which arises from the smooth muscle, but with immunohistochemistry of kit mutation and electron ultramicroscopy, now GIST is considered as a distinct tumor of mesenchymal origin(1). Identification of tyrosine kinase receptor KIT protein CD117 has been a very revolutionary step in identification of GIST as a different tumor. In this review, we described the epidemiology, diagnostic test, neoadjuvant therapy, surgery, adjuvant therapy, treatment of recurrent and metastatic disease of GIST (2).

2. Epidemiology

GIST is not common tumor of gastrointestinal tract it accounts for less than 3% of all GI tumors but it is a common soft tissue sarcoma. The reported incidence shows variation across the different part of world, studies which are conducted in US and other western countries has an incidence rate between 4 to 6 per million population whereas countries like China (Hong Kong) and Shanghai , and Korea has incidence rate of more than 10 per million (3). But the overall incidence across the world is not known. In a recent study included the 19 countries reported an incidence rate of 7 to 15 per million population.

The GIST typically involves the patients in their mid-60s. However, the GIST can occur in any age group, even younger individuals in their 20s are affected. GIST can involve any part of gastrointestinal tract from esophagus to the anal canal. The site which is most commonly reported is stomach (55%), followed by small intestine nearly 30%, large bowel around 5% and less 1% in esophagus. 10% of GIST are malignant and advanced stage at the time of diagnosis(4).

3. Familial

Familial GISTs and GISTs Syndromes

Familial GISTs, neurofibromatosis type 1 (NF1), Carney's triad (CT) and the Carney-Stratakis triad are the familial GIST syndrome which are associated with less than five percent of GIST. Familial GIST syndromes (FGS) show autosomal dominant type of inheritance (5). Familial GIST is usually common in families and most common site of involvement is small bowel where it presents as multiple small nodules.

Neurofibromatosis Type I (NF1)

GIST reported with neurofibromatosis type 1 in 7% and are associated with mutation in NF1gene that encodes neurofibromin (5). It is more common in female in comparison to male in their 50s. Gastrointestinal findings associated with NF1 are not as common as cutaneous one. NF1 related to GIST are several in number that occur in small intestine and these do not show mutation for kit gene but are immunohistological positive to kit mutation.

Carney *Triad*

This is another syndrome that is associated with GIST. Most commonly it occurs in female of young age in their 20s that typically presents with Gastric GIST, paraganglioma and pulmonary chondroma and shows higher incidence of lymphatic malignancy (5,6).

Carney Stratakis Syndrome

CSS associated GIST occur with equal predisposition to male and female, in age younger than that of patients with carney traids (6). Tendency of CSS related GIST is to be multiple in number and mainly involving the gastric region. These patients present with GIST, paragangliomas and pheochromocytomas. These tumors occur due to succinate dehydrogenase (SDH) enzyme mutation (genes *SDHA*, *SDHB*, *SDHC*, and *SDHD*). These individual shows absence of KIT and *PDGFRA* mutations.

Micro GIST

GIST with size less than 10 mm are mentioned as micro GIST (7). Proximal stomach and gastro esophageal junction are the most common site although it may occur at any site of GI tract.

4. Clinical Presentation

GIST has a wide range of clinical presentation which depends upon the tumor size, anatomical location and nature of tumor. Symptoms of tumor is directly proportional to its size. Tumor with size more than 5cm are mostly symptomatic in nature (5). Most common symptoms are GI bleeding, mass in abdomen and abdominal pain, gastric distress and ulcers. Cutaneous and soft tissue involvement is also rare in malignant GIST (8). Lymphatic metastasis is rarely shown by GIST thus regional lymph nodes are not enlarged. In many retrospective studies it is seen that small bowel GIST has a size larger than that of average gastric GIST and higher incidence of metastasis is associated with them in comparison to gastric GIST.

5. Investigation

The presentation of GIST is not specific, patients present with non-definitive symptoms, majority of case are diagnosed incidentally when imaging are done for any other pathologies. The National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) have given many guild lines for the diagnosis of GIST (9). Whenever a well circumscribed mass is identified in the gastrointestinal tract regardless of size, it is important to have GIST as differential diagnosis.

Abdominal ultrasound is the initial imaging performed in patient with abdominal pain or mass. GIST patients are further evaluated with contrast enhanced computed tomography (CECT) abdomen and pelvic in arterial as well as venous phases. In the CT scan finding these tumors appears as an enhanced mass which is well

circumscribed arising from the gastrointestinal tract. In the CT scan large tumors show heterogenous enhancement due to area of necrosis in the large tumors. Other advantages with the CT Scan includes the extent of tumor, metastasis in liver and peritoneal. Role of CT Scan is also seen in evaluating the response of GIST to the imatinib therapy, the tumor which respond to the imatinib show a homogeneous hypoattenuation pattern and less blood vessels, although Triphasic CT is better for hepatic metastasis detection.

Magnetic resonance imaging (MRI) is not superior to the CT Scan as an initial imaging technique, but Diffusion weighted MRI (DWI) results are comparable to that of PET and CT Scan. GIST being a metabolic active tumor, PET using 18F–fluorodeoxyglucose is used for both diagnosis and management. PET is used mainly in the metastatic tumor and to assess the response of tyrosine kinase inhibitor therapy. Traditional way of tumor response to the therapy was change in size in response to the treatment, with the use of PET Scan tumor metabolism is considered. And tumor which do not metabolic response to the therapy is indication of resistance. Now day's hybrid imaging method of FDG-PET and CT combinedly used.

Endoscopy plays a major role in the diagnosis and management of GIST and also helps in taking tissue for the pathological confirmation (10).

EUS has benefit of differentiating the intramural from extramural lesions along with it also tells the size, margin, echotexture and the lymph node status. EUS-guided fine needle biopsy (EUS-FNB) for histological assessment is also possible here.

6. Gross & Histology

GIST shows a large range of variation in the term of size, which ranges from few mm to more than 15cm. As the tumor arises from the muscle it is friable in nature (11). GIST has a normal mucosa over it, and they are well circumscribed tumor, some time they may have pseudo capsule with the growing size it out reaches its blood supply and shows necrosis, cystic degeneration and evident of hemorrhagic foci.

Histologically GIST has been divided into mainly three types.

Spindle Cell Type

These are most common histologically type and nearly seventy to seventy five percent. These histologically spindle cell tumor show peripheral enhancement with central hypodensity radiologically on CT Scan (12). Typical KIT and PDGFR mutation is mainly present in spindle cell type and therefore these types of tumor respond very well to the imatinib mesylate and hence they have best prognosis overall.

Epithelioid Cell Type

Histologically this type of tumor is less common with fifteen to twenty percent, but they don't show augmentation on CT scan and they do not possess KIT and PDFGR mutation (12). This tumor is more common in young age group. This type of tumor shows involvement of lymph as metastasis which is not seen in spindle cell type.

Mixed Type

They contribute nearly 10% of GIST tumor and they have combination of both type of tumor epithelioid and the spindle cells.

7. Immunohistochemistry (IHC)

GIST is mesenchymal tumor of gastrointestinal origin, it's not a very uncommon tumor, it shows genetic characteristic of KIT and immunohistologically shows the CD117 expression in about 80% to 90 % cases. KIT is a Tyrosine kinase molecule across the cell membrane, and it act as a receptor for stem cell (13). Activation of kit through dimerization occur on binding of stem cell to the receptor which in turn activate the intracellular pathway which is a

transduction signal pathway mainly RAS-RAF-MAPK and P13K-AKT-m TOR pathways. Mutation associated with kit proto oncogene mainly involves the four main exons, exon 11,exon 9,exon 13 and exon 17.

CD117/Kit

Most of the GIST tumors are positive for the CD117/KIT, but small percentage of these tumor are negative for CD117/KIT. Tumor marker like S100 show organ specific immunohistochemical response like they are positive in small intestinal GISTs than gastric GISTs (14). KIT is not specific to the GISTs, but it is positive in many other tumors.

CD 34

Majority of GIST tumor of gastric origin are positive to CD34 but only half that of small intestinal GIST tumor shows positivity to CD34 (15). Histologically the spindle type of GIST tends to show higher propensity to stain with CD34.

DOG 1

DOG 1 (Discovered on GIST 1) is an important biomarker in the detection of GIST, it has a high sensitivity and specificity for diagnosis of GIST. For the diagnosis of gastric GIST with epithelioid morphology having PDGFRA mutation DOG1 gene has higher sensitivity than KIT gene (14,15). GIST with spindle cell morphology has a better sensitivity for DOG 1 than GIST with epithelioid morphology. DOG 1 has a sensitivity over 90% to 95% for the GIST having high mitotic counts. DOG 1 marker has a better sensitivity than KIT specially GIST having PDGFRA mutation.

Protein Kinase C Theta

Immunohistological markers plays important role in the diagnosis of GIST cKit (CD117). Many times, a GIST which poses the Kit /PDFGA mutation but does not show positivity to the immunohistomarker like CD117 are misdiagnosed and proper line of treatment (Imatinib) is not given to patient which may have been given if patient is correctly diagnosed. So alternative immunohistological markers like DOG1 and Protein kinase C Theta (PKCθ) can be used in the diagnosis of GIST which are Kit /CD117 negative (16).

PDGFR Alpha

Mutation that involves PDGFRA gene in GIST are rare in comparison to that of Kit, these mutations constitute nearly 5% cases of GISTs. Pathway involved (MAP kinase and PI3K/AKT) in PDGFRA is similar that of Kit in the genesis of GIST but the receptor site of action is different. Both the Kit and PDGFRA mutations are mutually exclusive to each other. Exons involved are 18,14 and 12 (17).

Mutation involving the exon 18 is the most common involving PDGFRA more than 75% of PDGFRA mutation involves exon 18 which are missense substitution in which Asp is substituted by Val.

PDGFRA act on the ATP binding site thereby inhibit the imatinib action. So, tumor having these mutations are resistance to the imatinib therapy (18). Mutation involving the exon 14 is the next common which shows substitution mutation and are better than other exon mutations in term of prognosis. Mutation involving the exon 12 are not common in comparison to the other exon they rare one to occur.

Wild Type

Wild type of GIST is a variety of GIST which do not show KIT or PDGFRA mutation and constitutes 5% to 10% of GISTs. These tumors show less response to imatinib therapy and follow some another path for showing mutation. The wild GIST which have the SDH deficiency they use the insulin like signal pathway for the tumor progression and they are present in stomach only.

There are two type of wild GIST one with SDH deficiency and the other one which don’t have SDH mutation.

The one which have deficiency of SDH gene are having mutation in SDH subunit SDHA, SDHB, SDHC, SDHD are common in stomach(18-19).

8. Molecular Genetics

The most important step in the molecular biology of GIST is the identification of KIT and PDGFR mutation which lead to the introduction of imatinib. GIST has been seen showing good response to imatinib. Most common mutation exon 11 of KIT mutation often shows good response to imatinib (19). While patients that harbor exon 9 mutation tends to show less response to the imatinib therapy.

Exon 11

Most common exon which is mutated in kit gene is present in exon 11 region is more than 75% times associated with GIST tumor and within exon 11 mutation, In frame deletion is the one which is most common(20). Another mutation which commonly occur is simple deletion and is related to poor outcome and shows higher chances of metastasis this mutation typically occurs in exon 11 and involves the Trp557 and Lys 558 codon.

Exon 9

Mutation in exon 9 is most common after exon 11 in Kit gene. Mutation which occurs in exon is nucleotide duplication, this mutation is common in small intestinal GIST. Mutation in exon 9 shows better response to the surgical resection of tumor. However they shows less response to the imatinib treatment (21,22).

Exon 13

Mutation involving the exon 13 of Kit gene is a rare mutation involving less than 1% of the cases, these mutations are basically the missense mutations in which Lys is being replaced by Glu rendering it to more malignant (23). These mutations of exon 13 are resistance to imatinib therapy and sunitinib is effective in these tumors.

Exon 17

Mutation with exon 17 is a rare one similar to that of exon 13 mutation involving less than 1% cases. It is seen that exon 17 mutations are more commonly involves the small bowel than any other part of gastrointestinal tract (23). The mutation with exon 17 shows resistance to imatinib therapy.

9. Neoadjuvant Therapy

Neoadjuvant therapy is an important part of treatment protocol for the survival of patient which is given in the preoperative period to those who have an unresectable tumor. Neoadjuvant therapy is indicated when there is presence of locally advanced disease, presence of tumor of large size, tumor which are present at site that are not easy to assess (duodenal and rectal) ,tumor with high risk of recurrence (high mitotic count).With the use of neoadjuvant therapy chances of recurrence, rupture of tumor decreases (24). Imatinib is the neoadjuvant drug that is used for the GIST which show unresectabilty, metastasis or recurrence because imatinib has a good antitumor efficacy. Standard dose at which it is used is 400mg this is the dose at which it shows the optimum effect. The duration for which neoadjuvant therapy is to be in preoperative period ranged from 6 month to 10 month.

The preoperative systemic therapy which is given in GIST is of two type

1. Neoadjuvant therapy
2. Tumor downstaging therapy in preoperative period.

Neoadjuvant therapy, this therapy is given in the patients having resect able tumors and neoadjuvant therapy improves the surgical outcome. Patients those have the large primary GIST tumors or the site of tumor is such that where we want to preserve the normal tissue and surgeons avoids doing the extensive dissection.

Preoperative tumor down staging therapy, this concept is used in the management of the unresectable tumors. GIST which are resectable for them the first line of treatment is still the surgery. Imatinib

as a neoadjuvant therapy has shown effectiveness in many studies but the time for which it should be used is still a matter of debate, it should be given as a neoadjuvant therapy as long as tumor shows response to it and patient can tolerate it without much side effect (24, 25). ESMO in 2009 advice that for maximum benefit as a neoadjuvant therapy imatinib should be used for a duration of 3 to 12 months.

Assessment of Response to Tyrosine Kinase Inhibitor (TKI)

Criteria for the assessment of response to the treatment should be sound enough, quantifiable and meaningful, so that a better treatment can be given with its help and the treatment which is effective should be given. The Response Evaluation Criteria in Solid Tumors (RECIST) given decade ago for the response evaluation, here the tumor is measured in 1 dimension (26).

Recently the RECIST 1.0 is modified while keeping the same fundamental in to RECIST 1.1. The modifications done is the reduction in target lesions which denotes the tumor burden (5 in total and 2 per organ) and lymph node involvement. The Southwest Oncology Group (SWOG) gave criteria for the assessment of response to target therapy and the response is based on two parameters, one is measurable disease and other one is evaluable disease (27).

The choi criteria is better in terms of sensitivity and specificity when compared to the RECIST and SWOG, it takes into the account the tumor size and the density of tumor.

GIST being a metabolic active tumor, PET using 18F–fluorodeoxyglucose is used for the assessment of response of this metabolic active tumor.

Choi criteria which are used for the assessment of response to the treatment in the GIST patients, is more accurate and shows the better sensitivity when compare to the RECIST criteria.

Many studies have established the response shown by choi criteria, unidimensional reduction in the size of tumor by 10% or decrease in density of tumor on CECT by 15%, related directly with fine response by PET.

10. Surgery

The guidelines issued by the US National Comprehensive Cancer Network (NCCN)and the European Society for Medical Oncology (ESMO) mentions main goal for the surgical treatment is the R0 resection of GIST.

With the recent advances like tyrosine kinase inhibitors used as a targeted therapy in the treatment of GIST, still the curative treatment for primary GIST is the surgical resection. Surgical resection done for the operative cases should be plan in such a way so that complete resection of tumor can be done with the maximum possible way to preserve the organ involved (28). While performing the surgical resection care should be given not to breach the pseudo capsule and avoid rupture of tumor otherwise tumor seedlings will get deposited in the peritoneum. Outcome in term of recurrence is same for both whether resection done is R0 or R1 (29). While performing surgical resection of the stromal tumor aim should be to achieve a 1 to 2 cm of tumor free margin.

With the modern era where much of conventional open surgery is been replaced by the minimal invasive technique, role of minimum invasive surgery in surgical resection of GIST is indicated provided that the same oncological principal that of open surgical resection is followed. As the surgical experience increased in the laparoscopic surgical resection, small GIST of size around 2 cm were easily resected initially, according to the recent studies data tumor with size less than 5cm can be resected well through minimally invasive technique in experience hands (30).

11. Prognostic Factors

GIST malignancy which mainly involves the gastrointestinal tract shows revolutionary response to the Imatinib

therapy (Tyrosine kinase inhibitors) with the detection of KIT and PDGFR mutations. Recently many international guidelines has been issued by NCNN, ESMO and EURACAN for the prognostic factors in GIST and these are mitotic rate, tumor size and tumor site apart from these three other factors which are consider in some resent studies for the prognosis are high ki67,gastrointestinal bleeding and different gene mutations (31).

Recent version of NCCN guideline, the ESMO/EURACAN guideline and FICP guidelines proposes four prognostic factors which are important, and these are mitotic rate , size of the tumor ,site of tumor and the whether tumor rupture is present or not (32). Similarly, NCCN and FICP taken nomogram and contour in assessing the prognosis of GIST. But the most commonly used classification in clinical practice is AFIP classification and the Modified-NIH (M-NIH) classification.

Ki67 is also recently use factors in the prognosis of tumor, it denotes the proliferation of tumor cell and Ki 67 level more than 5% indicates the poor prognosis in terms of recurrence and metastasis.

12. Risk Assessment in Gastrointestinal Stromal Tumors

The main aim of the risk stratification system is to provide correct road map for the treatment of GIST tumors, with the introduction of tyrosine kinase inhibitors (imatinib) therapy complete change in the treatment of GIST has occur, however surgery is still the mainstay of treatment for the localized GIST. Recent trails in the past are evident that adjuvant therapy has a benefit in the high-risk cases after surgical resection (33).

Risk Stratification Systems

NIH Consensus Criteria

Fletcher et al. (34) develops the NIH criteria for the GIST. Fletcher used the two pathological factors size of the tumor and the mitotic count of tumor in order to classify the recurrence risk as very low, low, intermediate, or high (35). Later on, many other studies were done, and it was found that the tumor site along with the tumor size and mitotic count has prognostic important.

American Forces Institute of Pathology Criteria

The American Forces Institute of Pathology (AFIP) criteria were developed after a long period of follow up and analyzing the data of GIST patients. AFIP criteria includes the tumor site in addition to the size and the mitotic count because it was seen in many studies that GIST which arises from the gastric region has a better prognosis than that arises from the other region of gastrointestinal tract. AFIP includes the tumor size, tumor site and mitotic count (36).

Modified NIH Criteria (Joensuu Risk Criteria)

Joensuu has brought a modification the existing NIH system for the risk assessment in GIST. This modification includes the rupture and the location of the tumor. So, this system overall takes into account four prognostic factors i.e. tumor size, site, mitotic count and tumor rupture (37). Tumor rupture is taken as independent prognostic factor in addition to tumor size, site and mitotic count.

Prognostic Nomograms

A Nomogram is a mathematical way /model that can be utilized to predict the chances of recurrence of tumor. Gold nomogram was based on the retrospective study over 299 patients over 20 years of duration. Gold et al.(38) gave a nomogram for the likelihood of recurrence free survival (RFS), the nomogram takes in to account the size, mitotic count, and site of tumor in order to predict the 2 and 5-year RFS (39). Rossi et al.(39) also proposed a nomogram which is based on the size of tumor, mitotic count, and site of tumor..

Mutational Status

Certain GSIT harbor mutations in KIT and PDGFRA that are known to have prognostic values. Like exon 9 mutation and exon 11 deletions in KIT gene has a poor prognosis, and D842V mutation in PDGFRA is known to show the resistance to the imatinib therapy (41).

13. Adjuvant Therapy

Requirement of adjuvant therapy in GIST is due to high post-surgical recurrence rate in these tumors and patients having advance disease which are unresectable and metastasis or patients with recurrence do not show response to the chemotherapy. For the treatment of GIST many biologic agents are present as an adjuvant therapy. Many tumors respond very well to the tyrosine kinase inhibitors but some are not sensitive to the therapy and some show high risk of recurrence (KITgene exon 11 deletion), so genetic typing is always be done in order to predict the response to therapy (42).

Imatinib

As an adjuvant therapy, standard of choice for GIST is imatinib. Imatinib mesylate a tyrosine kinase inhibitor has shown a good response when used in metastatic GIST. Many studies done have advocated the use of imatinib for recurrent, locally invasive, or metastatic GIST, with not much serious side effect.

Response to the imatinib vary among the GIST. GIST harboring the mutation in exon 11 of KIT gene respond very well to the imatinib therapy. While those having the mutation in the exon 9 Ala502_Tyr503Dup show less response to the imatinib therapy (43). Similar is the condition with GIST having SDH gene deficiency they are also resistant to the adjuvant therapy, so patients harboring these mutations and having the localized disease surgical resection should be done but they show problem of recurrence (44).

Sunitinib Malate

Most of patient's response well to imatinib therapy while some tumor does not respond well, and shows refractoriness to the imatinib, these refractory tumors have shown efficacy to the sunitinib. Sunitinib is a multkinase inhibitor which is multitargeted activity and used in tumor growth, angiogenesis of tumor, metastatic disease (45). It inhibits the both platelet derived factor receptors (PDGFRA, PDGFRB), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3(FLT3),colony-stimulating factor receptor type 1(CSF-1R) and glial cell-line-derived neurotropic factor receptors(RET).

Regorafenib

Regorafenib another tyrosine kinase inhibitor which is multitargeted is been used in patients which are refractory to the imatinib and sunitinib therapy. This is used in case of locally advanced and GIST which are unresectable that show low response to the (imatinib and sunitinib) (46).

Avapritinib

Another tyrosine kinase inhibitors that targets PDGFRA and PDGFRA D842 mutant and mutation involving exon 11 ,17 or both 11/17 KIT. This drug inhibits the transduction pathway and it also inhibit the tumor cell proliferation of the cell expressing the PDGFRA and c-KIT mutation (46,47). This drug is indicated for the patients having the PDGFRA exon 18 mutation and D842V mutations in the unresectable and the metastatic GIST. This drug is given in dose of 300mg PO day.

Ripretinib

Ripretinib is a broad-spectrum inhibitor drug. It is tyrosine kinase receptor (KIT) and platelet derived growth factor receptor -A (PDGFRA).

Adjuvant Treatment in Resistance GIST

Gastrointestinal stromal tumors (GIST) show functional gain in mutation in KIT and PDGFRA. These above mentioned

mutations are important for the initiation and progression of tumor, so target of therapeutic agents are the KIT and PDGFRA. First line of target therapy is imatinib while sunitinib and regoratinib are the second and the third line of target therapy respectively.

For patients with GIST tumor imatinib has been used as an adjuvant treatment. GIST with the PDGFRA mutation and the SDH deficient mutation are seen to show less response to the imatinib as an adjuvant treatment. Mechanism which play role in the development of resistance to imatinib are as

- A new point mutation occurs in KIT and PDGFRA
- Genetic amplification of KIT
- Alternate activation of kinase pathway
- Loss of expression of KIT

Sunitinib malate came in role after the disease has progress to advanced level or the patients do not show response to the imatinib. Sunitinib is a multi-targeted TKI along with anti-tumor and antiangiogenetic properties. It is a VEGFR inhibitor and it act on different type of the tyrosine kinase inhibitors like FLT3,KIT,RET,PDGFR and VEGFR1,2,3 (48).

Regorafenib which are active against GIST possessing the resistance to the imatinib therapy, involves either the ATP binding pocket or the loop activation. GIST with KIT mutation involving the exon 11 respond to the Regorafenib. Loop activation of KIT kinase in imatinib resistance mutation are inhibited by the regorafenib, which shows resistance to the sunitinib therapy (49).

14. Treatment of Recurrent and Metastatic Disease

The key treatment in the GIST which shows metastasis and recurrence is imatinib therapy which causes disease free propagation. Many studies are conducted to find out the role of surgery in metastatic or recurrence GIST. Result of many studies suggested that tumor which were treated with the Multidisciplinary therapy (MDT) showed better outcome in form of progression free survival (PFS) and overall survival (OS) in comparison to the those treated with imatinib therapy alone. Surgery in advanced GIST is beneficial only if complete resection of tumor is done after imatinib therapy, where as simple debulking has no survival benefit (50).

Another point of debate is the duration of imatinib therapy, it is advisable to take the imatinib even after three years of treatment (51). Once the patient develops the toxicity to imatinib, second line tyrosine kinase inhibitors are given which includes sunitinib, regoratinib etc.

Newer agents in the treatment of GIST

Over several years, a lot of research and development have occurred in the treatment modality of GIST, with the discovery of CD117 role in GIST. Imatinib possessing the tyrosine kinase inhibiting activity. Patients with the advanced GIST and metastatic GIT responds to imatinib therapy. Sunitinib which act by targeting the multiple tyrosine kinase has an anti-angiogenesis action. Nilotinib was used in patients with advanced or metastasis GIST which failed to show response to imatinib and the sunitinib, but no significant response was seen. However, another known tyrosine kinase inhibitor of kit and PDGFRA, Dasatinib with antitumor activity was found to show the partial response. A multi kinase inhibitors with antitumor activity, Regorafenib have seen to show response to the advance GIST which were treated in the past with the imatinib and sunitinib. Mastinib a novel tyrosine kinase inhibitor shows activity greater than that of imatinib against the wild GIST and KIT mutation which are juxta membrane, and can be used in advanced, in operable, metastatic and locally advanced as a first line of therapy. Another agent is Crenolanib is high potency selective PDGFRA tyrosine kinase inhibitor against D842V mutation. Motesanib which is a VEGF, PDGF and KIT inhibitors have been used in trial in multicenter study for the imatinib resistant

GIST (51,52). The adverse effect which are associated with it are the hypertension, fatigue and diarrhea. PTK787/ZK222584 is another agent which is a selective tyrosine kinase inhibitor in the advanced GIST which shows imatinib therapy resistance (52).Hsp90 inhibitor have an antitumor effect in the GIST which shows the resistance. Ganetespib (STA 9090) and Retaspimycin hydrochloride (IPI504, a Hsp90 inhibitor) is a potent, synthetic inhibitor of Hsp90, which are under trial.

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REFERENCES

1. Kim M-Y, Jung H-Y, Choi KD, Song HJ, Lee JH, Kim DH, et al. Natural history of asymptomatic small gastric subepithelial tumors. J Clin Gastroenterol. 2011;45(4): 330–6.
2. Parab TM, DeRogatis MJ, Boaz AM, Grasso SA, Issack PS, Duarte DA, et al. Gastrointestinal stromal tumors: a comprehensive review. J Gastrointest Oncol. 2019;10(1):144–54
3. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomarkers Prev. 2015;24(1):298–302
4. Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer. 2005;117(2):289–93.
5. Coe TM, Fero KE, Fanta PT, Mallory RJ, Tang C-M, Murphy JD, et al. Population-based epidemiology and mortality of small malignant gastrointestinal stromal tumors in the USA. J Gastrointest Surg. 2016; 20(6):1132–40.
6. Nishida T, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet. 1998;19(4):323–4.
7. Antonescu CR. Gastrointestinal stromal tumor (GIST) pathogenesis, familial GIST, and animal models. Semin Diagn Pathol. 2006;23(2):63–9.
8. Briggler AM, Graham RP, Westin GF, Folpe AL, Jaroszewski DE, Okuno SH, et al. Clinicopathologic features and outcomes of gastrointestinal stromal tumors arising from the esophagus and gastroesophageal junction. J Gastrointest Oncol. 2018;9(4):718–27.
9. Faigel DO, Abulhawa S. Gastrointestinal stromal tumors: The role of the gastroenterologist in diagnosis and risk stratification. J Clin Gastroenterol. 2012; 46(8):629–36
10. Nishida T. The role of endoscopy in the diagnosis of gastric gastrointestinal stromal tumors. Ann Surg Oncol. 2015;22(9):2810–1.
11. Ducimetière F, Lurkin A, Ranchère-Vince D, Decouvelaere A-V, Péoc'h M, Istier L, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PLoS One. 2011;6(8):e20294.
12. Güler B, Özyılmaz F, Tokuç B, Can N, Taştekin E. Histopathological features of gastrointestinal stromal tumors and the contribution of DOG1 expression to the diagnosis. Balkan Med J. 2015;32(4):388–96.
13. Barnett CM, Corless CL, Heinrich MC. Gastrointestinal stromal tumors: molecular markers and genetic subtypes. Hematol Oncol Clin North Am. 2013;27(5):871–88.
14. Miettinen M, Killian JK, Wang Z-F, Lasota J, Lau C, Jones L, et al. Immunohistochemical loss of succinate dehydrogenase subunit A (SDHA) in gastrointestinal stromal tumors (GISTs) signals SDHA germline mutation. Am J Surg Pathol. 2013;37(2):234–40.
15. Lopes LF, West RB, Bacchi LM, van de Rijn M, Bacchi CE. DOG1 for the diagnosis of gastrointestinal stromal tumor (GIST): Comparison between 2 different antibodies. Appl Immunohistochem Mol Morphol. 2010;18(4):333–7
16. Bümming P, Ahlman H, Andersson J, Meis-Kindblom JM, Kindblom L-G, Nilsson B. Population-based study of the diagnosis and treatment of gastrointestinal stromal tumours. Br J Surg. 2006;93(7):836–43.

17. Joensuu H, Wardelmann E, Sihto H, Eriksson M, Sundby Hall K, Reichardt A, et al. Effect of KIT and PDGFRA mutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib: An exploratory analysis of a randomized clinical trial. JAMA Oncol. 2017;3(5):602–9.
18. Serrano C, García-Del-Muro X, Valverde C, Sebio A, Durán J, Manzano A, et al. Clinicopathological and molecular characterization of metastatic gastrointestinal stromal tumors with prolonged benefit to frontline imatinib. Oncologist. 2019;24(5):680–7.
19. Gold JS, Dematteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model: The gastrointestinal stromal tumor model. Ann Surg. 2006; 244(2):176–84.
20. Ramaswamy A, Bal M, Swami R, Shetty O, Bose S, Pai T, et al. Early outcomes of exon 11 mutants in GIST treated with standard dose Imatinib. Ann Transl Med. 2017; 5(6):134.
21. Lasota J, Corless CL, Heinrich MC, Debiec-Rychter M, Sciot R, Wardelmann E, et al. Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases. Mod Pathol. 2008; 21(4):476–84.
22. Antonescu CR, Sommer G, Sarran L, Tschernyavsky SJ, Riedel E, Woodruff JM, et al. Association of KIT exon 9 mutations with nongastric primary site and aggressive behavior: KIT mutation analysis and clinical correlates of 120 gastrointestinal stromal tumors. Clin Cancer Res. 2003;9(9):3329–37.
23. Bednarski BK, Araujo DM, Yi M, Torres KE, Lazar A, Trent JC, et al. Analysis of prognostic factors impacting oncologic outcomes after neoadjuvant tyrosine kinase inhibitor therapy for gastrointestinal stromal tumors. Ann Surg Oncol. 2014;21(8):2499–505.
24. Tirumani SH, Shinagare AB, Jagannathan JP, Krajewski KM, Ramaiya NH, Raut CP. Radiologic assessment of earliest, best, and plateau response of gastrointestinal stromal tumors to neoadjuvant imatinib prior to successful surgical resection. Eur J Surg Oncol. 2014;40(4):420–8.
25. Wada N, Kurokawa Y, Nishida T, Takahashi T, Toyokawa T, Kusanagi H, et al. Subgroups of patients with very large gastrointestinal stromal tumors with distinct prognoses: a multicenter study: Very Large GIST with Distinct Prognoses. J Surg Oncol. 2014;109(2):67–70.
26. Rutkowski P, Gronchi A, Hohenberger P, Bonvalot S, Schöffski P, Bauer S, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol. 2013;20(9):2937–43.
27. Zhang F-B, Shi H-C, Shu Y-S, Shi W-P, Lu S-C, Zhang X-Y, et al. Diagnosis and surgical treatment of esophageal gastrointestinal stromal tumors. World J Gastroenterol. 2015;21(18):5630–4.
28. Cameron S, Beham A, Schildhaus H-U. Current standard and future perspectives in the treatment of gastrointestinal stromal tumors. Digestion. 2017;95(4):262–8.
29. Nishida T, Blay J-Y, Hirota S, Kitagawa Y, Kang Y-K. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer. 2016;19(1):3–14.
30. Peng F, Liu Y. Gastrointestinal stromal tumors of the small intestine: Progress in diagnosis and treatment research. Cancer Manag Res. 2020;12:3877–89.
31. Lamba G, Ambrale S, Lee B, Gupta R, Rafiyath SM, Liu D. Recent advances and novel agents for gastrointestinal stromal tumor (GIST). J Hematol Oncol. 2012; 5(1):21.
32. Choi H. Critical issues in response evaluation on computed tomography: lessons from the gastrointestinal stromal tumor model. Curr Oncol Rep. 2005; 7(4):307–11.
33. Yoshikawa K, Shimada M, Kurita N, Sato H, Iwata T, Morimoto S, et al. Efficacy of PET-CT for predicting the malignant potential of gastrointestinal stromal tumors. Surg Today. 2013;43(10):1162–7
34. Fletcher CDM, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33(5):459–65
35. Hølmebakk T, Bjerkehagen B, Boye K, Bruland Ø, Stoldt S, Sundby Hall K. Definition and clinical significance of tumour rupture in gastrointestinal stromal

tumours of the small intestine: Rupture of gastrointestinal stromal tumours of the small intestine. Br J Surg. 2016;103(6):684–91.
36. Zhou C, Duan X, Zhang X, Hu H, Wang D, Shen J. Predictive features of CT for risk stratifications in patients with primary gastrointestinal stromal tumour. Eur Radiol. 2016;26(9):3086–93.
37. Kim H-C, Lee JM, Kim KW, Park SH, Kim SH, Lee JY, et al. Gastrointestinal stromal tumors of the stomach: CT findings and prediction of malignancy. AJR Am J Roentgenol. 2004;183(4):893–8.
38. Gold JS, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, Smyrk TC, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol. 2009;10(11):1045–52.
39. Rossi S, Miceli R, Messerini L, Bearzi I, Mazzoleni G, Capella C, et al. Natural history of imatinib-naive GISTs: A retrospective analysis of 929 cases with long-term follow-up and development of a survival nomogram based on mitotic index and size as continuous variables. Am J Surg Pathol. 2011;35(11):1646–56.
40. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PWT, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009; 373(9669):1097–104.
41. Jager PL, Gietema JA, van der Graaf WTA. Imatinib mesylate for the treatment of gastrointestinal stromal tumours: best monitored with FDG PET. Nucl Med Commun. 2004;25(5):433–8.
42. Tamborini E, Bonadiman L, Greco A, Albertini V, Negri T, Gronchi A, et al. A new mutation in the KIT ATP pocket causes acquired resistance to imatinib in a gastrointestinal stromal tumor patient. Gastroenterology. 2004;127(1):294–9.
43. Wada N, Kurokawa Y, Takahashi T, Hamakawa T, Hirota S, Naka T, et al. Detecting secondary C-KIT mutations in the peripheral blood of patients with imatinib-resistant gastrointestinal stromal tumor. Oncology. 2016;90(2):112–7.
44. Zheng S, Huang K-E, Pan Y-L, Zhou Y, Pan S-D, Li X, et al. KIT and BRAF heterogeneous mutations in gastrointestinal stromal tumors after secondary imatinib resistance. Gastric Cancer. 2015;18(4):796–802.
45. Mulet-Margalef N, Garcia-Del-Muro X. Sunitinib in the treatment of gastrointestinal stromal tumor: patient selection and perspectives. Onco Targets Ther. 2016;9: 7573–82.
46. DeMatteo RP, Ballman KV, Antonescu CR, Corless C, Kolesnikova V, von Mehren M, et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (alliance) intergroup phase 2 trial. Ann Surg. 2013;258(3):422–9.
47. Joensuu H, Martin-Broto J, Nishida T, Reichardt P, Schöffski P, Maki RG. Follow-up strategies for patients with gastrointestinal stromal tumour treated with or without adjuvant imatinib after surgery. Eur J Cancer. 2015;51(12):1611–7.
48. Benjamin RS, Casali PG. Adjuvant imatinib for GI stromal tumors: When and for how long? J Clin Oncol. 2016;34(3):215–8.
49. Ford SJ, Gronchi A. Indications for surgery in advanced/metastatic GIST. Eur J Cancer. 2016;63:154–67.
50. O'Neill AC, Shinagare AB, Kurra V, Tirumani SH, Jagannathan JP, Baheti AD, et al. Assessment of metastatic risk of gastric GIST based on treatment-naïve CT features. Eur J Surg Oncol. 2016;42(8): 1222–8.
51. Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol. 2012;13(3):265–74.

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