Gastrointestinal Stromal Tumour - A Paradigm Shift in Management of Solid Tumours

PP Bapsy*, K Prabhash**, KG Babu,***, MH Girish**

Abstract

Gastrointestinal stromal tumour (GIST) till recently were non-responsive to all chemotherapy agents. With the advent of c-kit, diagnosis of GIST has become more specific. STI-571, a tyrosine kinase, has become one of the first targeted therapeutic agent to be active in solid tumour. At present it is the only agent with substantial activity in GIST.

INTRODUCTION

Gastrointestinal stromal tumour (GIST) term was coined to refer collectively to a group of mesenchymal neoplasm in gastrointestinal tract. This term was used extensively with uncertainty over the histogenesis of tumour. Historically in 1940s stromal tumours were regarded as smooth muscle tumour (term usually used were leiomyoma, leiomyosarcoma, etc.). The introduction of electron microscope in late 1960s revealed that most of these tumours did not show ultrastructural evidence of smooth muscle differentiation. Immunohistochemistry in 1980s confirmed that many of these cases lack immunophenotypic features of smooth muscle differentiation. In 1983 a more generic designation stromal tumour was coined.1 Subsequently it was termed as plexosarcoma and gastrointestinal autonomic nerve tumour (GNAT).

In 1990s confusion increased. It was observed that 60-70% of GISTs are CD34 immunophenotype positive but CD-34 positivity has also been observed in Schwann cell and the smooth muscle tumours.2 Subsequently observation concerning KIT mutations and KIT expression has clarified many doubts regarding diagnosis. STI-571 (imatinib mesylate) a molecular targeted therapy in GIST has completely changed the treatment approach for this patients.

BIOLOGY OF KIT ACTIVATION

KIT immunoreactivity defines a group of tumours being derived from (or showing differentiation towards) interstitial cells of Cajal. They are also called as pacemaker cells. This forms the interface between autonomic innervation of bowel and smooth muscle. Most of the mesenchymal tumours are now classified as GIST. Carefully analyzed GNAT has been found to share molecular identity with GIST. GNAT should no longer be considered as a separate entity.3

KIT is transmembrane tyrosine kinase receptor. Its extracellular domain binds a ligand and intracellular portion contains kinase enzymatic domain. Normally KIT activation occurs after the ligand binds to the extracellular domain. This leads to homodimerization of the receptor activating the KIT kinase domain. Activated kinase crosstalkphosphorylates tyrosine homodimer partner leading to further activation of receptor. The phosphorylated tyrosines binds various cell-signaling proteins, which leads to activation of various cell-signaling pathways. They control cell proliferation, adhesion, apoptosis and differentiation. KIT expression is high in hematopoietic stem cells, mast cells, melanocytic cells, germ cells and the interstitial cells of Cajal (ICC) in gastrointestinal tract. ICC is a complete network of innervated cells located between peripheral nervous system and smooth muscle cells in gastrointestinal tract. ICC arises from uncommitted mesenchymal cells. KIT expression plays important role in differentiation, proliferation and formation of functional ICC network.4

Activation of KIT in tumour is not dependent on KIT ligand. Structural changes in KIT oncoprotein leads to their uncontrolled activation. KIT mutation has been found to be most important mechanism for KIT activation in tumours. KIT mutation is present in around 92% of GIST. In 71% cases frame mutation occurs in exon-11, 13% cases frame duplication occurs in exon-9, 4% cases point mutation occurs in exon-17 and in 4% of cases point mutation occurs in exon-13.5

These mutations can be of two types. First is enzymatic pocket or enzymatic site mutations. Second type is regulatory type mutation. In regulatory type mutation normal amino acid sequence of enzymatic site is preserved. This classification can be useful in predicting drug resistance and guiding treatments. Tumours with mutation in regulatory site and normal enzymatic site respond to the tyrosine kinase inhibitor...
STI-571, which bind well to native kinase enzyme. Patients with mutation in kinase enzyme do not respond well to STI-571 because it does not bind well to mutated enzymes. Resistance to STI-571 can also be due to amplification of gene. This amplification can be overcome by increasing the dose of STI-571. Resistance may also occur due to additional mutation not known to us at present.

There are few GISTs in which mutation in KIT region has not been identified. In these cases most common reason remains technical consideration. Genomic alteration in the non-coding regions of the KIT gene or alteration in the expression or function of proteins known to modulate the KIT cell signaling pathways may be the additional mechanism for KIT activation. Other than KIT mutations aberrant activity of proteins interacting with KIT or shift in balance of KIT isoforms can also be additional factors. In less than 5% of cases of GIST do not express KIT. It has been suggested that they might express alternate receptor tyrosine kinase oncprotein related to KIT.

**Cytogenetics**

Chromosomal changes are common in GIST. Most karyotypes in GIST are simple as compared to other spindle cell tumours. Benign GISTs usually have normal karyotype or have isolated loss of chromosome 14. Borderline malignant GISTs have loss of chromosome 14, usually associated with loss of 1p, 9p, 11p or 22q. High grade GIST usually contain at least three of the above mentioned chromosomal deletion. In these high-grade GIST also karyotype remains substantially less complex than leiomyosarcoma, undifferentiated sarcoma or malignant peripheral nerve sheath tumour. Chromosomal rearrangement targeting KIT locus in GISTs has not been documented. In a study of 94 GIST patients, 24 with low-grade disease had mean number of chromosomal aberration of 2.6, 36 high grade GIST and 35 metastatic GIST had mean number of chromosomal aberration of 7 and 9, respectively.

**Diagnosis**

It is now evident that KIT is clinically and therapeutically important in GISTs. Pathologists has had consistent result using commercially available antibodies to KIT (CD117) on paraffin-embedded sections. Now it is recommended that terminology GIST should be used for neoplasm showing KIT immunopositivity with rare exceptions.

The exceptions are - patient with typical histopathological features of GIST but KIT negative due to :
1. Sampling error
2. Test done following STI-571 treatment
3. Fixation artifact
4. < 2% patient who lack either KIT mutations and/or KIT overexpression.

   Tumour in these categories should be labeled as spindle or epithelioid stromal neoplasm most consistent with GIST.

   As with all immunostaining, KIT positivity should not be seen in isolation for diagnosing GIST. It must always be interpreted in light of microscopic features. KIT immunostaining should be used to confirm the diagnosis and determination of eligibility for STI-571 therapy. A very few other types of sarcoma may show KIT positivity (e.g. - pleomorphic sarcoma) but more often they are due to technical artifact.

   Histologically majority of cases of GIST have classical uniform appearances. There are three types of GIST - spindle cell (70%), epithelioid (20%) and mixed type.

   GIST can arise anywhere in the gastrointestinal tract. Epithelioid lesion occurs more often in stomach. KIT expression has shown that similar lesion can occur in mesentery, retroperitoneum, gall bladder and urinary bladder. 50-60% of GIST occurs in stomach, 20-30% in small intestine, 10% in large intestine, 5% in oesophagus and 5% anywhere in the abdominal cavity.

**Prognosis**

Prognosis of GIST depends on many factors. Most of these factors are not well defined. Factors considered for prognoses are :

* Clinico-pathological:
   * Tumour stage - Liver and peritoneal metastasis confer adverse prognosis as compared to small serosal tumour detected incidentally.
   * Tumour site - GIST in colon and rectum usually presents in more advanced stage as compared to GIST of stomach and rectum. GIST of omentum might be less aggressive than mesentery GIST.
   * Tumour size and mitotic activity - They are the most important prognostic factors. They should be applied together.
   * Cellularity - Low cellularity may be a favorable prognostic factors.
   * Muscle invasion - Invasion in smooth muscle has no prognostic significance.
   * Mucosal invasion - Mucosal invasion is rare, but if seen signifies malignant GISTs.
   * Ulceration - This is mainly related to tumour size. Ulceration has no prognostic significance.
   * Immunohistochemical differentiation - The rate of CD34 positivity has no prognostic significance. Actin expression is more commonly seen in benign intestinal GIST.

**Genetic Markers**

1. Gain or loss of genetic material : In general low risk tumours are diploid and high-risk tumours are aneuploid. Loss of DNA on short arm of chromosome 1 has been identified in malignant GISTs.
2. Telomerase activity : Telomerase activity is almost exclusively seen in malignant GIST. Additional studies
are needed to validate this finding.\textsuperscript{12}

3. KIT - Activating mutation: Identifying specific KIT mutation may help in identifying patients who will respond to STI-571. Value of KIT as a prognostic factor is controversial.\textsuperscript{10}

It is now widely accepted that almost any GIST has potential to behave in malignant fashion. GIST workshop at National Institute of Health (NIH) on April 2 to 3, 2001 recommended a gradation of risk for an aggressive clinical course.

Risks were defined as\textsuperscript{2} -

1. Very low risk - this is defined as tumour size of less than 2 centimeter with mitotic count less than 5 per 50 high power field.
2. Low risk - this is defined as tumour size of 2 to 5 cm with mitotic count less than 5 per 50 high power field.
3. Intermediate risk is tumour size of less than 5 cm with mitotic count 6 to 10 per 50 high power field or tumour size of 5 to 10 cm with mitotic count less than 5 per 50 high power field.
4. High risk is tumour size of more than 5 cm with more than 5 mitotic count per 50 high power field or tumour size of more than 10 cm or more than 10 mitotic count per high power field.

**MANAGEMENT OF GISTs**

The development of STI-571 has revolutionized the treatment of GIST. STI-571 inhibits KIT tyrosine kinase activity, which acts on a specific molecular target in GISTs. As a result of this GIST now serve as the model solid tumour for a molecular biology based diagnosis and treatment.

**Surgery**

Surgery is the primary treatment for GIST. Complete resection without rupturing the tumour is the primary aim. Lymphadenectomy, a standard procedure in intestinal adenocarcinoma, is not recommended because GIST rarely metastasized to lymph nodes. For localized disease 5-year survival of 54% has been reported. Tumour more than 10 cm have 5-year survival of only 20%.\textsuperscript{13}

**Adjuvant therapy**

Observation is usually recommended after complete resection. As 5-year survival after resection remains 54% only, but effective adjuvant treatment is not available at present. Radiation therapy may have a role in with positive surgical margin in gastric or rectal GIST.\textsuperscript{14}

**METASTATIC DISEASE**

At MDACC only 10% of patients remain disease-free after extended follow up. The disease usually recurs in peritoneal cavity and/or the liver. Median survival is only 15 months after the resection of recurrent GIST.

**Systemic chemotherapy**

Response rate of metastatic GIST appears to be less than 10%. The various chemotherapeutic agents used are doxorubicin, dacarbazine, ifosfamide, cisplatin, etoposide, and epirubicin without much benefit. The resistance of GIST to chemotherapy may be due to increased level of P-glycoprotein, multidrug resistance protein and oncogenic activation of KIT.\textsuperscript{14}

**Intraperitoneal chemotherapy**

Recurrence in peritoneal cavity is most common. Intraperitoneal chemotherapy becomes attractive in this situation. Intraperitoneal chemotherapy with cisplatin and adriamycin has been used. Mitoxantrone has been used intraperitoneally with encouraging results.\textsuperscript{15}

**Radiation therapy**

Radiotherapy is useful in palliation. This has been useful in bleeding and pain due to GIST.

**STI-571 in metastatic disease**

Most anticancer therapies have evolved in late 1990. A small molecule known as STI-571 selectively blocks the ABL kinase and kill CML cells in vitro. This was first published in 1996. Data from clinical trials in CML were published in early 2001.\textsuperscript{16} In may 2001 the US Food and Drug Administration approved this molecule for CML patients. It was also identified that STI-571 can also block the enzymatic activity of tyrosine kinases of KIT and PDGFR. In a phase II trial of STI-571 in GIST, 145 patients were included in the study. The doses used were 400 or 600 mg every day. The partial response was observed in 59% of patients and 13% of patients progressed on treatment.\textsuperscript{17}

A second phase II trial conducted by EORTC (European Organization for Research and Treatment of Cancer) included 36 patients in the study. They observed response rate of 69% and progression was seen in 11% of patients. FDA has approved STI-571 for the use in metastatic GIST.\textsuperscript{18} This is the first drug that has significant activity against this tumour. This drug has become a role model for development of further drugs acting at molecular level in solid tumours. The major toxicities of STI-571 includes mild fatigue, weight gain, periorbital edema, diarrhea and muscle cramps. Gastrointestinal bleeding has been reported in a few patients which could be due to massive tumour necrosis by the drug.

**STI-571 as adjuvant therapy**

The role of STI-571 is being evaluated in adjuvant setting because of marked activity in metastatic disease. It may have greater impact on survival when there is minimal disease. There are at least two trials going on in adjuvant setting. One of these trial is in phase II and other is in phase III, both of them is being conducted by American College of Surgeons Oncology Group (ACOSOG). Radiation Therapy Oncology Group (RTOG) is conducting a phase II trial in neoadjuvant setting. Results of these trials are eagerly awaited which will have significant impact on GIST management.\textsuperscript{14}

**STI-571 current and future**

STI-571 has become the first line agent for metastatic GIST. Patients refractory to STI-571 should be considered for
traditional palliative treatment. (e.g.- hepatic artery embolization, radiation therapy, surgical debulking or intraperitoneal chemotherapy).

It is very clear that STI-571 has major impact on the management of patient of GIST. We should also recognize the challenges ahead in the management of these tumours. The new challenges are -

1. STI-571 rarely leads to complete response and significant percentage of patients does not respond at all. Future research will explain why certain cells die and others survive.

2. As new molecular discoveries are coming in, it becomes essential to have new molecular therapy for GIST resistant to STI-571.

3. STI-571 also inhibits PDGFR. STI-571 might be effective in tumours with higher expression of PDGFR. Recent data suggest activity of STI-571 in dermatofibrosarcoma protuberans, which has increased expression of PDGFR.19

Traditional chemotherapy has reached its maximum benefit in most of the hematological and solid tumours. Targeted therapy has been found to be effective in hematological tumours. In solid tumours targeted therapy has been found to be effective in GIST and carcinoma breast in metastatic setting. Targeted therapy is being tried in other solid tumours. In future they are going to be the area of reasearch.

REFERENCES