GASTROINTESTINAL STROMAL TUMOUR PROGNOSTIC PARAMETERS: CASE REPORT AND LITERATURE REVIEW*

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ABSTRACT

This paper reviews the evaluation of malignancy and prognostic parameters used in gastrointestinal stromal tumours (GIST). Incorporated is a case report of a duodenal GIST treated at our institution. GIST represents a spectrum of mesenchymal tumours from benign to malignant variants, which can arise from anywhere in the gastrointestinal tract. A central pathogenetic event recognised in most GISTs is KIT activation (a tyrosine kinase receptor) believed to be the result of oncogenic mutations. Imatinib mesylate, (a humanised monoclonal antibody), highly effective in vitro in reducing KIT tyrosine activity, has revolutionised the treatment of metastatic GIST, and is discussed along with other treatment options. Traditionally the three key prognostic factors used in GIST have been mitotic rate, tumour size, and anatomic location. However, the unpredictable behaviour of GIST has led to the development of immunohistochemical differentiation markers including CD117 (detecting KIT protein). In addition genetic markers have been used as prognostic parameters, including KIT activating mutations, cytogentic aberrations and telomerase activity.

Case report

A 53-year-old male farmer presented with a three-day history of epigastric pain and melaena, preceded by a syncopal episode. For two weeks previously he had taken an NSAID for a painful shoulder. His GP found him hypotensive and arranged transfer to A & E, where he was haemodynamically stable, blood was found per rectum and Hb was 88g/l. He was commenced on IV omeprazole and underwent gastroscopy that revealed a 1cm dome-shaped tumour with a central bleeding ulcer, in the descending duodenum. This was injected with 10ml adrenaline (1:10,000) and the patient transfused with two units of packed cells. Two days later Hb was 85g/l and he was again transfused two units of packed cells. Repeat gastroscopy enabled biopsy of the tumour, which proved to be a gastrointestinal stromal tumour. CT scan showed a 3cm component of this tumour indistinguishable from the pancreas, at the level of the third part of the duodenum.

The patient underwent laparotomy with local complete excision of the tumour and duodenal repair. Histological examination showed a spindle cell stromal tumour 13mm in diameter, with mitotic rate of 0.5 mitoses per 10HPF and no evidence of necrosis was observed. Immunohistochemistry demonstrated positive staining to CD34, Neuron Specific Enolase (NSE), and Vimentin consistent with diagnosis of GIST. CD117 immunostaining was not available at this institution.

Discussion

GIST were most often classified, until recently, as leiomyomas and leiomyosarcomas, but are now known to represent a discrete neoplastic entity[1]. The term GIST, proposed by Mazur and Clark in 1983, was first used to classify all gastrointestinal non-epithelial mesenchymal tumours[2]. GIST are the most common mesenchymal neoplasms of the gastrointestinal tract, typically expressing KIT (a tyrosine kinase receptor)[3]. GIST arising in the muscle wall usually between the muscularis propria and muscularis mucosae may expand towards the bowel lumen, the serosa or in both directions[4]. Clinically and pathologically, GIST represents a spectrum of tumours from benign to malignant.

GIST incidence peaks in the fifth and sixth decades, is rare before 40 years, but can occur in the paediatric population[5,6,7]. GIST have been estimated to comprise between 0.1% to 3% of all GI malignancies[7,8], 20% of small bowel malignancies and 0.1% of large bowel malignancies[9]. GIST most commonly arise within the wall of the stomach (40-70%) and the small intestine (20-40%) and rarely in the oesophagus, colon and rectum (5-15%)[5,6], or duodenum (4%)[10]. There may be a greater incidence in men[4] while others note no sex difference[3,5]. The effect of gender on tumour behaviour is uncertain; some suggest it does not influence tumour behaviour[11]; others associating male sex with markedly poorer prognosis and increased occurrence of metastases[12].

At diagnosis about 40% of GIST are less than 1.5cm and asymptomatic[4]. Of symptomatic GIST up to 86% are associated with GIT bleeding (acute or chronic)[4,8]. In decreasing frequency the presenting symptoms are abdominal mass, GIT bleeding, anorexia, dysphagia, and obstruction[13,14].

The interstitial cells of Cajal (ICC), localised in the myenteric plexus believed to act as a gastrointestinal pacemaker cell governing peristalsis have been proposed as the cell of origin[5], supported by several immunohistochemical and ultrastructural similarities[3,15,16,17]. Alternatively, GIST may originate from precursor stem cells that can differentiate toward either a smooth muscle or ICC phenotype[7], with KIT expression believed to be crucial in encouraging differentiation of these cells towards an ICC endpoint[18].

Tumours with ultrastructural characteristics of GI autonomic nerve tumours (GANT) are also GIST tumours, based on their KIT positivity and presence of essentially identical KIT activating mutations[3,19]. GANT are believed part of the neoplastic spectrum of stromal tumours, displaying a higher degree of ICC differentiation[16]. GANT should no longer be regarded as a separate entity[20].

GIST are thought to occur by mutations of the KIT gene, located on the long arm of chromosome 4 expressed in the cells of Cajal (ICC)[21]. ICC are immunostained by antibodies against KIT (CD117)[22]. KIT encodes a transmembrane tyrosine kinase receptor, consistently expressed in GIST[6].

Structurally, the KIT receptor can be divided into four principal regions (domains): an extracellular domain; a transmembrane domain; a juxtamebrane domain; and a kinase domain separated into two sections. KIT gene mutations, irrespective of the domain for which they code, cause the receptor to be activated without its ligand (stem cell factor (SCF)), resulting in a continued stimulus for cell proliferation[23].

The KIT gene sequence has 21 exons, and in sporadic GIST, the majority (50-77%) of KIT mutations have been found in exon 11, encoding the juxtamembrane domain of the receptor[3]. A germline mutation identified in familial and multiple GIST has also been identified in the juxtamembrane domain[24]. GIST with exon 11 mutations were originally reported to be of a higher grade, or associated with poorer outcomes[15,25,26]. Subsequently, exon 11 mutations were believed to hold prognostic value. Further, mutations have been described in exons 9 (extracellular domain), 13 and 17 (the two kinase domains)[1,25,27,28] with the majority of exon 9 mutations associated with highly malignant GIST[25,28]. The significance, if any, of exons 13 and 17 is overshadowed by their infrequent[1,25,27] or non-expression[15] in reported GIST series.

Overall, the estimated frequency of KIT mutations is between 21% and 92%[7]. Failure to analyse the entire KIT coding sequence, and limitations encountered with some PCR assays used, as well as genetic differences between series populations may account for this variation[1,15]. A number of GIST, although lacking KIT mutations demonstrate strong KIT activation. Presumably KIT mutations, in these instances, have been detected by conventional screening methods, or, other non-mutational mechanisms may have led to KIT activation. Consequently it has been suggested oncogenic KIT activation occurs in the earliest stages with progression to more malignant behaviour determined by successive cytogenetic and molecular changes[18].

The majority of GIST are the result of somatic mutation. Rare familial cases have been described, however predisposing factors are unknown[3]. A link to EBV infection[4], association with Carney's triad (paraganglioma, pulmonary chrondroma, and leiomyoblastoma of the stomach, a very rare syndrome mainly affecting young women)[29], and association between GIST and Von Recklinghausen's syndrome have been reported[8]. The pathogenetic link between NF1 and GIST may be purely casual[30].

Morphological parameters

While mitotic count appears to be the most reliable indicator overall of GIST behaviour, with a high count correlating to malignant behaviour[31,32] there are accounts detailing GIST, with low mitotic counts behaving aggressively[8,23]. Mitotic count correlates poorly with the malignant potential of small bowel GIST[33]. A major criticism of mitotic counts has been their subjectivity and poor reproducibility[34].

Grading systems have been devised with different cut-off points for the number of mitoses per 10 HPF[6,7]. Mitotic count per 50 HPF is now recommended[19]. Tumours with 0-1 mitoses per 10-50 HPFs will not give rise to metastases, those with more than 5 mitoses per 50 HPFs are considered malignant[13,19]. A mitotic rate ≤ 5 mitoses per 50 HPF is commonly used as a limit for a tumour of predicted benign behaviour. However this cut off point fails to discriminate between benign and malignant small intestinal tumours[33].

Tumour size is suggested as more important than histology in predicting behaviour[4]. Almost all small (<1cm) GIST are clinically benign; tumours more than 5cm are generally malignant[3], however no cut-off diameter predicts malignant behaviour with certainty. For duodenal tumours malignant behaviour is more likely in tumours greater than 4.5cm[31,35].

Prognosis in GIST also varies with anatomic site, but the degree to which this relates to tumour size and/or histologic subtype is not clear. Purportedly, anatomic location is a prognostic factor independent of tumour size, mitotic rate and patient age[36]. Most duodenal GIST occur in the second part of the duodenum, with duodenal and small intestinal GIST more likely to display malignant behaviour relative to gastric GIST[38]. Small bowel tumours have the worst prognosis and oesophageal the best[23,38].

Histologically, GIST express a variety of cell types and growth patterns. Either of two cell types may predominate (spindle cells and epithelioid cells)[5], however a mixed cell type may occur[11]. Spindle cell-type form the majority comprising 70-80% of gastric tumours along with the majority of small intestinal GIST[6]. Epithelioid lesions occur more often in the stomach. Lesions of mixed cell type may exhibit an abrupt transition between spindle and epithelioid cells, however there may an intermediate cytologic appearance[36]. There are some site-specific variations in morphology with spindle cell lesions of the small bowel having a tendency to contain skenoid fibres[37,38]. Skenoid fibres formerly believed to correlate with neural differentiation, now appear to have no histogenetic significance[36]. Correlation of histologic pattern with prognosis is not established[11], nor is predominant cell type related to pattern of antigenic expression[12].

Rather than using distinct benign and malignant categories, GIST should be regarded as having some malignant potential, described in terms of risk assessment[32] (low, intermediate or high risk), so that no lesion can be definitively labelled as benign.

Immunohistochemical differentiation markers

Immunohistochemistry has been a fundamental tool in the diagnosis of GIST. The antibodies commonly used to characterise GIST are those directed against CD34, CD117 (KIT protein), vimentin, desmin, smooth muscle actin (SMA), S100 protein, and neuron specific enolase (NSE).

GIST are usually positive for CD117 and CD34[36,37], variably positive for smooth muscle actin, and usually negative for desmin[23,36]. Antibodies to CD34 and CD117 differentiate GIST from smooth muscle and other intestinal mesenchymal tumours[6,16].

CD34 reactivity is seen in a wide range of normal tissues and tumours. CD34 is expressed in 60-70% of GIST[36]. A recent large series found CD34 positivity to have no prognostic significance. However, CD34 may aid in distinguishing gastrointestinal leiomyomas and schwannomas, which are negative for CD34[16]. Furthermore, CD34 in combination with CD117 and S100 can be used to differentiate GIST from most other mesenchymal tumours[5]. It also has been shown to demonstrate a reciprocal relationship with SMA expression – CD34 positive tumours are often SMA negative[17]. The variability of CD34 staining among GIST may be due to several phenotypes of GIST precursor cells (ICC)[16].

CD117 is now accepted as the most specific immunohistochemical marker for GIST[39]. CD117 is expressed in 80-100% of GIST and is not expressed in smooth muscle (leiomyoma, leiomyosarcoma) or neural tumours (schwannomas)[3,5]. CD117 positivity is seen in all histologic variants and in benign and malignant GIST of different sites[6]. Nevertheless some maintain that positive CD117 is not absolutely required in all cases of GIST[37]. Interestingly, the detection of KIT expression (by immunohistochemical staining with CD117) does not indicate KIT gene activation.

The lack of unanimity with respect to the immuno-markers used may be a reflection of case selection bias[5]. Although a specificity and sensitivity issue with the antibody(s) used has to be considered.

Genetic markers

Prognoses using genetic markers are currently being defined. The detection of overall net losses and gains of genetic material initially focused on flow cytometry with benign tumours generally diploid and malignant tumours aneuploid. A correlation of aneuploidy with poor prognosis had been suggested[11]. The frequency of aneuploidy in GIST ranges from 22-60%[40]. Ploidy patterns appear to have failed in reliably separating benignity from malignancy. It remains unproven whether DNA ploidy patterns are an independent prognostic marker for GIST. Aneuploidy may be associated with a mere tendency to an adverse outcome[12].

Molecular cytogenetic screening, particularly with CGH, reveals correlations between acquisition of chromosomal aberrations and aggressive clinicopathologic behaviour[18]. CGH enables screening of tumour genomes for gains (representing oncogenes) and losses (suggesting tumour suppressor genes) of DNA and their consequential mapping to chromosomal

subregions[41]. Losses are more likely related to the development of GIST, whereas accumulation of additional genetic alterations, particularly gains/amplifications, is required for malignant transformation and metastatic behaviour in GIST[42].

The most convincing support of CGH-detected DNA copy changes as prognostic markers came from a recent series of 95 GIST, including 24 benign, 36 malignant primary, and 35 metastatic tumours[42]. The mean number of demonstrable chromosomal aberrations found were (2.6) benign GIST, (7.5) malignant GIST and (9) metastatic GIST. Deletions of chromosome arms 1p, 14q, and 22q were frequent irrespective of histologic grade. However, 9p deletion, 8q amplification, and 17q amplification were found almost exclusively in malignant GIST. LOH and FISH analyses have also supported the finding of chromosome 9 losses occurring preferentially in malignant GIST[19]. According to El-Rifai et al[42] the absence of gains can be considered a good prognostic parameter, suggesting it can be used as a new complementary diagnostic criterion for GIST. Undoubtedly, some DNA copy changes will prove to have more prognostic significance than others. No correlations between any specific DNA copy number changes and tumour location were found[42].

Although the cytogenetic profile in GIST is often distinctive, with characteristic chromosomal deletions (typically involving chromosomes 14 and 22)[41,42], none of the individual chromosomal aberrations appear specific to GIST. It has been argued for this reason that cytogenetic studies are less crucial than histopathology, KIT immunohistochemistry, and KIT molecular analyses in the routine evaluation of GIST[18].

Telomerase, an enzyme implicated in maintaining the de novo synthesis of the ends of eukaryotic chromosomes is expressed in 80-90% of carcinomas[43]. Its activation is a hallmark of carcinogenesis, with continued renewal of the chromosomal ends by telomerase thought to be a mechanism favouring cell proliferation[44]. Telomerase activity, a negative prognostic indicator, has been investigated in two studies (a total of 42 GIST cases)[43,44]. Unique to malignant GIST, telomerase activity was not detected in benign cases from either series, although not all malignant cases expressed telomerase. Gunther et al[44] showed a primary GIST tumour initially with no telomerase activity, which displayed marked activity in its recurrence. This phenomenon of late activation of telomerase has been reported previously[45]. Telomerase cannot yet be viewed as a reliable prognostic indicator.

Treatment and management

Until recently there was no effective therapy for unresectable or metastatic GIST, which is invariably fatal. A major development in treatment of advanced GIST has been the use of imatinib mesylate (Glivec), approved by the US Food and Drug Administration in 2002, for treatment of patients with CD117 positive unresectable and/or metastatic malignant GIST[46]. Imatinib mesylate works by inhibiting tyrosine kinase activity[47] which is believed to be the basis behind the neoplastic proliferation of GIST. Its use in non-metastatic GIST or for neo-adjuvant therapy is not established.

Complete surgical resection is the primary therapy for GIST, but the required extent of resection, including regional lymph nodes or adjacent organs remains unclear[7]. No benefit has been reported from obtaining wide margins[37]. Failure to obtain histologically tumour-free margins is associated with adverse outcomes[3]. Regional lymph node dissection is of unproven value[36].

Metastases occur in more than 50% of patients diagnosed with malignant or high-risk tumours at the time of resection[37]. Propensity for local recurrence suggests a role for adjuvant therapy, however data is lacking in support of the use of either radiation or chemotherapy[3,13]. Pierre et al[7] found that patients receiving adjuvant therapy had worse outcomes. Radiotherapy is limited by potential toxicity to surrounding structures[23] and is not standard post-operative therapy for GIST.

There is wide variation in five-year survival rates, 19-56% overall and 32-63% following complete resection[7]. Most recurrences occur within five years of primary treatment, but can appear more than 10 years after treatment[3], indicating the need for long-term follow-up.

The difficulty in identifying reliable prognostic parameters only adds further confusion to the already controversial topic of gastrointestinal stromal tumours. Classifying GIST based on clinical presentation and morphology alone is difficult if not impossible, with the criteria for malignancy based on tumour size and mitotic count dependant on tumour location. Immunostaining for CD117 (although not entirely specific, but sensitive for GIST) along with a panel of antibodies, supplemented with careful morphologic examination assists the diagnostic process. The reported frequency and prognostic value of KIT activating mutations is uncertain, and in some instances contradictory. Results from molecular cytogenetic studies, suggesting a possible correlation between clinicopathologic behaviour and chromosomal aberrations, have significantly aided the defining of new prognostic parameters. Cytogenetic aberrations appear to be secondary events to oncogenic mutations. The possibility of particular aberrations uniquely affecting signaling pathways, and thereby determining the pathway of GIST progression remains to be seen. Telomerase expression, exclusive to malignant GIST (although not always expressed) may occur as a late event. Its validation as a useful prognostic marker depends heavily on the recruitment of larger numbers of cases and extended clinical follow-up.

This review has highlighted the inconsistencies of current prognostic parameters used in GIST. A multiparametric approach is necessitated, as no sole prognostic indicator has yet been determined reliable. The true test of any chosen parameter is one that can predict outcome on an individual case basis.

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