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GASTROINTESTINAL STROMAL TUMORS (GISTS): DIAGNOSIS AND TREATMENT

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INTRODUCTION:

Gastrointestinal Stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Their cellular origins are found in cells of Cajal which are responsible of the induction and regulation of peristalsis and smooth muscle (1). GISTs are rare in the soft tissue sarcomas but have particular interest because since the 2000s enormous progress was performed about:

Nosological identification by molecular biology
Endoscopic and radiological studies.
Knowledge of prognostic factors.
Development of targeted therapies

All this has led to a significant improvement of prognosis with a median survival that goes from 12 to 50 months in the metastatic setting.

Evolution of concepts and carcinogenesis:

Recent years have experienced a revolution in the understanding of oncogenesis of these tumors. GISTs were first classified as conjunctival tumors based on the histogenesis. The development of immunohistochemistry (IHC) allowed to orientate the diagnosis into muscular origin based of Actin positivity, neurogenic origin by the positivity of the PS100 and mesenchymal origin by CD34 positivity. However no specific markers of this cell line was available . (2)

The 2000s were marked by a revolution in the understanding of GIST by identifying the c-KIT and its expression by IHC CD117. The c-KIT is a trans-membrane tyrosine kinase receptor that once linked to its specific ligand SCF (stem cell factor) will trigger a signaling cascade leading to activation of apoptosis, differentiation, and cell adhesion. GISTs are characterized by an activating mutation of the ckit which will cause uncontrolled cell proliferation and resistance to apoptosis. (3)

The second step in the understanding of oncogenesis of GIST was reached due to advances in molecular biology with the identification of activating mutations that will often concern the KIT or PDGFRa genes. The search for these mutations will allow the positive diagnosis and having prognosis and predictive factor of response to treatment. (4)

Epidemiology

The annual incidence is of around 2000-5000 cases / year in the United States and 400-600 cases / year in France. The average age is 40 to 60 years with some pediatric cases remaining exceptionals. The sex ratio is 1.

The majority of GIST are sporadic and rare syndromic forms are describe Carney disease, the type 1 nurofibromatose and some exceptional family forms . (5,6)

The topographic distribution is as follows:

- Stomach: 60%
- Small intestine: 25%
- Colon and rectum: 5 to 10%
- Esophagus and mesentery, omentum : 5%.

Histology:

GISTs will know a exophytic endophytic or in hourglass growth. It are pseudo- encapsulated, firm, rounded with clear limits. The size is variable. GISTs may be whitish, encephaloid with occasional hemorrhagic or necrotic alterations.

Three main histological forms are described: fusiform in 70% of cases, epithelioid in 20%, and mixed form in 5% of cases . Other histological variants are rare (in peliomorphes cells, myxoid form ...)
GIST is classically defined as mesenchymal tumors of the digestive tract expressing CD117 in immunohistochemistry. CD117 antigen expression corresponds to the transmembrane c -kit tyrosine kinase receptor, it is positive in 95% of GIST. (8)

DOG-1 is a protein of 986 amino acids of unknown function. It's often expressed at the plasmatic membrane of GISTs and is rarely expressed in other soft tissue tumors, which by their appearance can be confused with GIST. In a study immunoreactivity for the DOG-1 was reported in 97.8% of KIT- negative GISTs. (8)

The CD34 is a marker for hematopoietic and mesenchymal precursor cells. It is positive in 60-70 % of GIST and is a valuable diagnostic help.

Other markers can be useful in the diagnosis of GISTs: vimentin and smooth muscle actin are variably expressed by GIST and desmin is rarely present. In contrast, the true smooth muscle tumors often express high levels of desmin and smooth muscle actin.

The S-100 is used to distinguish GISTs from other tumors of neural crest such as melanoma and schwannomas . It is particularly useful to differentiate GISTs with a primary neuronal phenotype from schwannomas.

The research of KIT and PDGFRA genes mutations by molecular biology techniques, in addition to confirming the diagnosis in difficult cases, is now part of common practice in the treatment of GISTs. Genotype analysis of GIST is recommended except for GIST at very low risk of recurrence. The type of mutation influences the prognosis and treatment efficacy in the adjuvant and metastatic situations. Mutations of KIT and PDGFRA are variable in their topography on gene and nature (duplications, deletions, wrong direction ...). Mutations interesting the Kit gene are most common with 75% of cases. The mutation in exon 11 is most often detected (70% of cases), followed by exon 9 (5 to 10%) and less frequently mutations in exons 13 and 17. 10% of GISTs are mutated PDGFRa with mutations of exon 18 (5 to 10%), exon 12 (0.9%) and exon 14 (0.3%). Finally there is a heterogeneous group of GISTs called wild type with no detected KIT or PDGFRa mutations. (9) This group represents 15% of GIST and now rare mutations are identified affecting RAS pathway (BRAF, NRAS, HRAS), NF1 (Neurofibromin 1) gene, succinate dehydrogenase or IGFR (Insulin-Like Growth Factor Receptor) gene.

Diagnostic:

The clinical symptoms of GISTs depend on tumor location. Asymptomatic forms are discovered during routine endoscopic or radiological examination constitutes 20 to 30% of cases. Symptomatic forms have no specificity and will be discovered in case of occult digestive bleeding, pain or abdominal discomfort or dysphagia or rectal syndrome. Finally the complicated forms with intestinal obstruction, gastrointestinal bleeding or perforation are not exceptional. (10)

Endoscopic examinations will suggest the diagnosis by showing the appearance of submucosal tumors with sometimes ulcerated mucosa under their surface. Endoscopic-ultrasound is the best technique to differentiate GISTs from other submucosal tumors. GISTs have the characteristic appearance of hypoechoic lesion, oval, often homogeneous, with regular limits developed in muscularis.

Abdominal CT scan must be performed in multiphasic acquisition and characteristically shows exoluminal tumors, with clear limits, tissue density and variable homogeneity.

Other exams will be performed depending on the indications. MRI is the gold standard for GIST of the rectum and is more sensitive than CT for the evaluation of liver metastases. Ultrasound with contrast injection is a dynamic examination without radiation and allows early assessment of treatment response. It challenges therefore the indications of PET scanner.

Positive diagnosis is certainly histological. Biopsy can expose to bleeding risk and peritoneal dissemination when made by percutaneous or laparoscopic. The French National Digestive Cancer thesaurus (TNCD) believes that the biopsy is not necessary in case of easily resectable lesions. it becomes inevitable in case of diagnostic doubt with other tumors may require chemotherapy first, in case of local or metastatic extension making discuss initial treatment with Imatinib or in cases where surgery is important or mutilating.

Prognostic factors:

In localized stage, the indications of adjuvant therapy are based on prognostic classifications that assess the risk of relapse. The first published is that of Fletcher in 2002 (Table 1) taking into account two parameters: size and mitotic index. (11)

Miettinen et al. returns revise this classification by adding tumor location (Table 2). For example a gastric tumor mesurig 52 mm with a mitotic count of 3/10 HPFs will be classified as intermediate risk according to Flesher classification and only low risk in Miettinen. This classification would help identify the patient group with significant relapse risk who need adjuvant therapy.

This difference is well illustrated since for the same patient population (n = 1552) 980 (63%) was classified as high and intermediate risk on the classification Flecher against only 631 (41%) according to Miettinen. (12)

The concept of tumor rupture was introduced to this classification and switches automatically patients at high risk. (13)

Furthermore the detected type of mutation appears to be an important prognostic factor and should probably integrate prognostic classifications. Survival rate in localized phase varies considerably with the type of mutation detected. Progression-free survival are 26, 13, 16 and 11 months and median survival are 60, 31, 43 and 34 months respectively for the mutation of KIT exon 11, KIT exon 9, wild types and finally the other mutations. (14)

The type of mutation will influence even the response to treatment with Imatinib. (15)

Treatment:

Surgery:

The only curative treatment for localized GISTs is surgery which must be macroscopically complete, mono-bloc and without tumor rupture. Margins of 1 to 2 cm are sufficient and lymph node dissection is not routinely performed. The extent of resection will depend on the tumor location: atypical gastrectomy, segmental small bowel resection, total esophagectomy ... (16)

In metastatic situations the place of surgery is difficult to define. Few data are available and indications should be discussed in a multidisciplinary team with evaluation of risks-earnings ratio in case of.

- Occurrence of complications.
- Focal progression in diffuse disease controlled by tyrosine kinase inhibitors (TKI).
- Resectable metastases after response to medical treatment.

The study of Raut et al. published in the Journal of Clinical Oncology in 2006 shows the feasibility of surgical approach in metastatic GISTs with a survival benefit in case of a disease controlled by TKI. (17)

Medical treatment:

Adjuvant therapy:

Despite radical surgery relapse rate found in surgical series was very high (40% at 10 years). An adjuvant therapy was necessary to improve prognosis. (18)

IMATINIB (imatinib mesylate) is a protein tyrosine kinase inhibitor, which inhibits the Bcr-Abl tyrosine kinase at the in vitro, cellular, and in vivo levels. In addition, imatinib is an inhibitor of several receptor tyrosine kinases: the platelet-derived growth factor receptors (PDGFR- and PDGFR-), and the stem cell factor (SCF), receptor (c- Kit), and it inhibits the cellular events mediated by these receptors. In vitro, imatinib inhibits proliferation and induces apoptosis of cells of gastrointestinal stromal tumor (GIST), which express an activating mutation of the kit. (19)

The results of pivotal trial conducted by Dematteo et al. and presented at the annual meeting of ASCO (American Society of Medical Oncology) in 2007 constituted a revolution in the management of these tumors. The use of one year of adjuvant

imatinib after resection of GISTs showed an improvement in disease-free survival compared to placebo (97 vs 83% at 1 year) except for GISTs with low risk of relapse. Imatinib was approved in indication. (20)

The updating of the trial published in 2014 shows the continuation of benefit in disease-free survival without improving overall survival and the lack of interest of adjuvant therapy in low-risk patients. Analysis by subgroups shows that the benefit is significant only for GISTs with KIT mutation of exon11. The benefit was not statistically significant for GISTs with KIT exon 9 mutations, wild types or PDGFRa mutation. The D842V mutation in PDGFRa gene confers primary resistance to Imatinib. (21)

Three years of adjuvant Imatinib became the standard treatment for GISTs with high-risk of relapse following the results of the test conducted by Joensuu et al. comparing 3 versus 1 years of Imatinib. This trial demonstrates a significant gain in progression-free survival and overall survival with prolonged treatment. (22)

Neoadjuvant therapy

This approach is particularly important for potentially resectable GIST in case of response to Imatinib. This strategy is to discuss **all the cases** in a multidisciplinary team. Obtaining histological confirmation of the disease is obligatory. In this case medical treatment will be commenced first followed **by** surgery in the maximum response (6 to 12 months) and then adjuvant Imatinib for duration depending on histological finding. (23)

A phase 2 trial by the RTOG (Radiation Therapy Oncology Group) explores this strategy for locally advanced or in case of local recurrence or operable metastatic disease. The authors conclude that although this approach was feasible, a large percentage of patients progressed after treatment and probably we should propose a more prolonged treatment after surgery (duration of 2 years of maintenance Imatinib was used in this study). (24)

Treatment of metastatic forms

Overall survival rate at 1 year was increased from 50% with chemotherapy to 90% with Imatinib. A real evolutionary turning point in the management of these chemo-resistant tumors has been accomplished. The use of 400mg of Imatinib per day permits obtaining a median survival around 50 months in various published studies. (25)

Two **Phases** 3 studies have compared two doses of imatinib 400mg vs. 800mg per day for metastatic GISTs. The grouped analysis of these two trials showed a slight improvement in progression-free survival in favor of the 800 mg arm (23 Vs 19 months). The subgroups analysis based on mutations type showed that patients with KIT mutation in exon 9 derive maximum survival benefit with the use of the double dose (PFS 19 Vs 6 months). This group of patients should be treated immediately with 800 mg per day of Imatinib. (26)

The superiority of continuous treatment compared to intermittent treatment was established by the BFR14 trial. This is a phase 3 study randomizing patients with metastatic non-progressive GIST after 1, 3 or 5 years of treatment with Imatinib between a continuous treatment or interruption of treatment and its reintroduction in case of tumor progression. The results show a benefit of continuous treatment in progression-free survival with a lower incidence of secondary resistance. (27)

Rapid progression under Imatinib (usually less than six months from treatment starting) defines a primary resistance to Imatinib. There are exceptional primary resistances to Imatinib (less than 10% of cases) (28) and prior to retain this diagnosis it is essential to eliminate a number of situations:

-a false **progression:** therapeutic evaluation by conventional criteria (WHO, RECIST) is not suitable for patients with metastatic GISTs under Imatinib. An increase in size or appearance of lesions initially overlooked may erroneously lead to talk of progress (29)

Current recommendations are to use CT scan with density measurement, the FDG-PET or Doppler ultrasound with injection of microbubbles. CHOI criteria are validated for therapeutic evaluation for this indication. (30)

- A poor compliance by interviewing patients and possibly achieve a serum dosage of Imatinib. This exam is available in a few specialized centers. The threshold should theoretically be around 1000 ng / ml. (31)

The resistance of GIST Imatinib theoretically imposes two concepts: the need to better block the KIT target by increasing doses of Imatinib, or the emergence of resistant clones imposing the change of the inhibitor.

Two studies (EORTC 62005 and US S0033) have explored the strategy of increasing Imatinib doses to 800mg per day after progression under 400mg. These two studies showed a temporary benefit of this strategy in approximately 30% of patients. (32,33)

Sunitinb is a mulicibles tyrosine kinase inhibitor (VEGFR2, PDGFRa, RET, FLT3 and KIT). It was tested against placebo in a population of refractory or intolerants Imatinib patients. This was a phase 3 trial; double-blind with authorized cross-over that demonstrated a statistically significant survival benefit in favor of the experimental arm. (34)

REGORAFENIB is an oral agent that inhibits multiple protein kinases, including those involved in tumor angiogenesis (VEGFR1, 2, 3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E) and in the tumor microenvironment (PDGFR, FGFR). His interest in metastatic GISTs was established in 199 patients resistant to Imatinib and Sunitinb with a 73% reduction in the risk of progression during the study. (35)

Pazopanib is an powerful inhibitor of many protein-tyrosine kinase : receptors of vascular endothelial growth factor (VEGFR1, VEGFR2, and VEGFR3), receptors of platelet-derived growth factor (PDGFR and PDGFR) and the receptor stem cell factor (c-KIT). PAZOGIST was a randomized phase II study evaluating the efficacy of pazopanib + supportive care versus only supportive care in patients with metastatic and/or locally advanced unresectable GISTs refractory to imatinib and sunitinib. The results presented at the annual meeting of the ASCO in 2015 were positive in survival benefit. (36)

Conflict of interest:

All authors declare not have any competing interests in the manuscript.

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All authors have equally contributed to realization of this article.

Ethics, consent and permissions

- This study was approved by the ethics committee of military hospital of Raba

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