

ADJUVANT TREATMENT IN GISTS

Adjuvant Treatment in GISTS

Laercio Gomes LOURENÇO¹, Ricardo CAPONERO²

Work carried out in a ¹Escola Paulista de Medicina, Federal University of São Paulo and ²Hospital Heliópolis, São Paulo, Brazil.

ABSTRACT - Introduction - Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the digestive tract. This cancer occurs due to mutation of the KIT gene resulting in constitutive activation of KIT protein. The primary treatment is surgical and consists of complete resection. However, some groups of patients at high risk of recurrence even after surgery with complete resection (R0), indicate differences in biological behavior. Clinical studies have demonstrated the clinical activity of imatinib mesylate, making it the standard first-line treatment in metastatic or unresectable GISTS, changing the outcome of this disease in relation to the benefits obtained previously with cancer chemotherapy. **Methods** - Was performed a literature review with consultation in Medline/Pubmed, Lilacs and Scielo crossing the key words: gastrointestinal stromal tumor, GIST, treatment, adjuvant treatment. In addition to this review was added to the authors' personal experience. **Conclusion** - Better refinement of prognostic criteria is allowed to select the most appropriate patients for adjuvant treatment with imatinib. The results are yet evident on basis of one year, which produces significant benefit in relapse-free survival but not overall survival in these patients.

HEADINGS - GIST. Treatment. Adjuvant treatment. Gastrointestinal stromal tumor.

Correspondence:

Laercio Gomes Lourenço,
e-mail: llourenco.dcir@unifesp.br

Financial source: none
Conflicts of interest: none

Recived for publication: 09/09/2010
Accepted for publication: 22/02/2011

RESUMO – Introdução - O tumor estromal gastrointestinal (GIST) é o sarcoma mais comum do aparelho digestivo. Essa neoplasia ocorre devido à mutação do gene KIT com consequente ativação constitutiva da proteína KIT. O tratamento primário é cirúrgico e consiste na sua ressecção completa. Entretanto, alguns grupos de pacientes apresentam risco elevado de recorrência mesmo após operação com ressecção completa (R0), indicando diferenças no comportamento biológico. Estudos clínicos comprovaram a atividade clínica do mesilato de imatinibe, fazendo dele a primeira linha de tratamento padrão nos GISTS metastáticos ou irrissecáveis, mudando muito o desfecho clínico dessa doença em relação aos benefícios anteriormente obtidos com a quimioterapia antineoplásica. **Método** – Foi realizada revisão da literatura com consulta nos periódicos das bases Medline/Pubmed, Scielo e Lilacs cruzando os descritores: tumor estromal gastrointestinal, Gist, tratamento, adjuvância. Além desta revisão foi adicionada a experiência pessoal dos autores. **Conclusão** - Melhor refinamento dos critérios de prognóstico tem permitido selecionar de forma mais adequada pacientes para o tratamento adjuvante com imatinibe. Os resultados de maior evidência até o momento respaldam o tratamento adjuvante por um ano, o que produz benefício significativo na sobrevida livre de recidiva, mas não na sobrevida global desses pacientes.

DESCRITORES-Gist. Tratamento. Adjuvância. Tumor estromal gastrointestinal.

INTRODUCTION

The gastrointestinal stromal tumor (GIST) is the most common sarcoma of the digestive tract. This cancer occurs due to mutation of the KIT gene resulting in constitutive activation of KIT protein.

The primary treatment is surgical and consists of complete resection. However, some groups of patients at high risk of recurrence even after surgery with complete resection (R0), indicating differences in biological behavior. Today it is known that this risk varies from zero to 100%⁷ (Table 1). The risk of recurrence depends on several factors mainly the anatomical location of primary tumor (the stomach have a lower risk than those of the rectum), tumor mitotic index (<or ≥ 5 mitoses

in 50 CGA), tumor size (> 3 cm) and probably the presence of tumor rupture during operation. The detection of the primary site of the mutation in the tumor presents debatable prognostic role in patients without treatment with imatinib. However, the presence of exon 11 mutation is predictive of longer time to disease progression and survival compared to patients with mutations of exon 9, when treated with the same dose of imatinib^{4,5}.

TABLE 1 - Risk stratified by primary GIST of the mitotic index, size and location

Tumor parameters		Progression risk of disease			
Mitotic Index in 50CGA	Size in cm	Stomach	Duodenum	Jejunum / Ileum	Rectum
≤5	≤ 2	0%	0%	0%	0%
≤5	>2 a ≤ 5	1.9%	4.3%	8.3%	8.5%
≤5	>5 a ≤10	3.6%	24%	#	#
≤5	>10	10%	52%	34%	57%
>5	≤2	?	High	#	54%
>5	>2 a ≤5	16%	73%	50%	52%
>5	>5 a ≤10	55%	85%	#	#
>5	>10	86%	90%	86%	71%

= Insufficient data to estimate prognosis³

GISTs, changing clinical outcome of this disease in relation to the benefits previously obtained with cancer chemotherapy.

Once demonstrated activity in advanced disease, the logical step is to study the effect of medication as an adjuvant treatment in order to increase the time to progression and, preferably, the overall survival of patients, and at the same time investigating the potential of imatinib mesylate to increase resectability and decrease surgical morbidity when used preoperative (neoadjuvant).

In the clinical setting, patients with this disease are at risk of progression and death that approaches certainty. It is not described any cases of spontaneous remission. After the operation, however, only a portion of patients with relapsed evolve. Patients not cured by the operation will benefit from the use of imatinib. Patients with adverse prognostic factors may also have recurrent disease, being necessary to treat them.

Two questions are key in this situation. First, what is the risk reduction that can offer treatment (relative benefit) and, second, what is the risk that the patient runs. Reducing risk is what will give us the absolute benefit of treatment. Thus, estimating the risk of recurrence of GISTs is crucial.

To determine the safety of treatment and the potential for risk reduction, the American College of Surgeons Oncology Group (ACOSOG) conducted two clinical studies. A first phase II feasibility of treatment with imatinib in the postoperative period, and a second, randomized, phase III, placebo-controlled trial (ACOSOG - Z9001), which included 713 patients with GISTs resected (R0). These studies demonstrate that, besides being well-tolerated treatment, was observed lower rate of recurrence in the group that used one year of imatinib treatment (2%) compared to the placebo group (17%).

These findings led to the approval by the Food and Drug Administration U.S. (FDA) in December 2009, the name of imatinib as adjuvant treatment in patients with GIST, surgery, and classified as high risk of recurrence.

The evolution of knowledge about the biology of this disease has changed the prognostic evaluation over time. This is a difficult point, yet controversial, and therefore became a key detail in ongoing studies. The study Z9001, because of the knowledge available at the time, just considered the size of the tumor, which contributed to overestimate the risk in some patients with gastric GISTs, and underestimate the risk for tumors of the duodenal and rectal location.

In 2009, a consensus of the National Institute of Health (NIH) defined as high-risk tumors larger than 10 cm in diameter (regardless of mitotic index), tumors of any size with a mitotic index exceeding

METHODS

Was performed a literature review with periodic consultation in Medline / Pubmed, Lilacs and Scielo; across headings were gastrointestinal stromal tumor, GIST, treatment, adjuvant treatment. In addition to this review was added the author's personal experience.

The main sites of relapse are the liver and peritoneum. Most recurrences are rarely described in the abdominal lymph nodes, lungs and bones.

GISTs are tumors that develop most often from the mutation, with a gain of function, tyrosine kinase (KIT). However, this change does not seem to be sufficient or absolutely necessary. There are reports of stomach microGISTs (tumorlets), with KIT mutation who do not progressed to malignancy, as there were between 5% to 10% of GIST patients with malignant phenotype in the absence of changes in cKIT.

Imatinib mesylate (Glivec® - Gleevec®, Novartis Pharmaceuticals, Basel, Switzerland) is a molecule that is designed to bind the ATP binding site of the tyrosine kinase resulting in t translocation (q34, q11), which gives rise to the Philadelphia chromosome and Bcr-Abl tyrosine kinase. During the development of the molecule was observed also their ability to prevent tyrosine phosphorylation of KIT, PDGFR alpha and, in a lesser degree, other tyrosine kinase.

Progressive clinical studies (Phase I, Phase II and III) demonstrated the clinical activity of imatinib mesylate, making it the standard first-line treatment in metastatic or unresectable

10 mitoses per 50 CGA and even tumors larger than 5 cm with a mitotic index greater than five mitoses per 50 CGA. These criteria define a better group of patients who would benefit from the use of imatinib.

Later, the Institute of Pathology American Armed Forces (AFIP) included the anatomical location as a prognostic factor. However, neither the criteria of Fletcher (NIH), nor of Miettinen-Lasota (AFIP), considered the tumor rupture (spontaneously or by surgical manipulation). This situation is sorted by Joensuu⁶ as being important in the spread of disease in this case is to be classified as high risk of recurrence⁷.

Gold et al.⁵ proposed a nomogram to predict recurrence after complete resection of GISTs compound, as the criteria of the AFIP, three prognostic factors: tumor size, mitotic index and anatomical location. The difference is to allow treating risk as a continuous variable rather than categorical, predicting the recurrence rate in two and five years. This nomogram has been validated in two large series of GIST - Spanish Group for Sarcoma Research and the Mayo Clinic in Rochester, USA.

Despite progress in the refinement of prognosis still remain technical details that need to be better defined, for example, if the extent of the tumor should be considered before or after the surgical setting, where the diameter of the high-power field microscope where mitosis count, how to determine which areas of microscopy should be analyzed for mitosis, since there is no homogeneity tumor^{4,6,8}.

The mitotic count should be expanded because the current situation the number of five mitoses per 50 CGA is very critical and define risk groups very different. In duodenal GIST, for example, patients with tumors of the same size will have a recurrence risk of 4% to <5 mitoses in 50CGA or 60% if > 5 mitoses in 50CGA^{1,2,8}.

Another definition is needed of how long should adjuvant treatment. The Z9001 study showed benefit in reducing the risk of relapse at one year of treatment, but not overall survival gain demonstrated so far. There are several explanations for this, but one of them, supported by indirect evidence from other trials, is that one year of treatment may not be enough^{3,5}.

Three major studies are underway which compare two (EORTC / Intergroup) with three years (SSG / AIO) and another with up to five years (U.S. study). The forecast for disclosure of efficacy data from these studies is for the year 2015.

Another aspect that may explain the failure of gains in overall survival in the study Z9001 is the rescue of the placebo patients with surgical treatment and / or imatinib after recurrence. Patients receiving this drug had the same response when compared to the group received the medication from the beginning, and there is apparently detrimental to the survival of these patients.

CONCLUSION

Further refinement of prognostic criteria is allowed to select the most appropriate patients for adjuvant treatment with imatinib. The results of yet more evidence backing the adjuvant treatment for a year, which produces significant benefit in relapse-free survival but not overall survival in these patients.

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