

Treatment of non-resectable and metastatic gastrointestinal stromal tumors: experience with the use of tyrosine kinase inhibitors in a third level hospital in Mexico

Abdel Karim Dip Borunda, Alberto Pimentel Renteria, Miguel Pluma Jiménez, Mario Pérez Martínez, Gloria Martínez Martínez, Samuel Rivera Rivera, Rocío Grajales Álvarez, Yolanda Bautista Aragón, Miguel Quintana Quintana, Juan Alejandro Silva

Department of Medical Oncology, Oncology Hospital of the National Medical Center for the Mexican Institute of Social Security, Mexico City, Mexico

Contributions: (I) Conception and design: AK Dip Borund, J Alejandro Silva; (II) Administrative support: None; (III) Provision of study materials or patients: A Pimentel Renteria, M Pérez Martínez; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Abdel Karim Dip Borunda. Medical Oncologist at the Oncology Hospital of the National Medical Center for the Mexican Institute of Social Security, Mexico City, Mexico. Email: borund@hotmail.com.

Background: Stromal tumors of the digestive tract are uncommon malignant diseases, are subclassified as leiomyosarcomas and Gastrointestinal Stromal Tumors (GIST) depending on the molecular expression of tyrosine kinase receptor KIT (CD117). GISTs represent 1% of malignant tumors affecting this anatomical site. Localized tumours diseases are reasonably well controlled by surgical resection and several criteria define the need for adjuvant therapy. In the case of metastatic disease a poor prognosis has been reported with systemic treatment based on chemotherapy. Recently, significant advances have been shown since tyrosine kinase inhibitors (TKIs) were introduced, with median overall survival close to 5 years. Unfortunately in Mexico, even though the therapy has been long used there are no published data of the experience in the treatment of these tumors.

Methods: We used an electronic data base to obtain clinical, radiological and histological data of patients diagnosed with GIST and treated in the oncological center of the Mexican Institute of Social Security, patients were subclassified by stage, symptoms at diagnosis as well as the initial and subsequent systemic treatment. Finally we made an analysis for progression free survival and overall survival identifying prognostic factors.

Results: We obtained information of 71 patients with metastatic, non-resectable or recurrent GIST, treated with a TKI, we observed a predominant relation for women (60.4%) with median age of 58 years. Stage at diagnosis was predominantly metastatic (46.5%), most frequently affected sites were lung, liver and retroperitoneum. Median progression free survival was 30.6 months and overall survival was 81.3 months. All patients were initially treated with imatinib at a dose of 400 mg per day. Treatment was well-tolerated in most cases.

Conclusions: Metastatic GIST evaluated in our center shows a different affection in gender and age, and our population shows a different response to TKIs, compared to those reported in other series with superior overall survival. Poor prognosis is associated with lung affection. Biological studies will be started for the molecular evaluation of these tumors.

Keywords: Gastrointestinal stromal tumors (GIST); KIT; tyrosine kinase inhibitors (TKIs); immunohistochemical staining

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Introduction

Stromal tumors that affect the gastrointestinal tract are uncommon, representing about 1% of the overall cancer cases. Clinically, they present as subepithelial lesions. The group of highest frequency is formed by the gastrointestinal stromal tumors (GIST). The common locations for this tumor are gastric and small bowel level, however, they may develop at any portion of the digestive tract including the omentum, mesenterium, and peritoneum (1).

At the molecular level, this type of tumors are characterized by the expression of CD117, part of the KIT receptor, a membrane kinase produced by the KIT proto-oncogene, this expression has been reported in up to 80% of the GIST cases, however, there are mutations related to the over expression of other tyrosine kinase receptors, such as the platelet derived growth factor receptor alpha (PDGFRA) (2).

The treatment assays based on chemotherapy have demonstrated low efficacy in the management of non-resectable and/or metastatic tumors, showing a high rate of primary resistance to this kind of management (3).

The treatment of this type of patients experienced a radical change by the identification of the activating mutations and the subsequent introduction of molecular treatments, mainly targeted to the signaling pathways generated by KIT and PDGFRA.

Most of the treatment experience in tyrosine kinase inhibitors (TKIs) is based on imatinib mesylate, where the results of long term and large simple sized studies show significant increases of the progression free survival and on the overall survival, with acceptable toxicity in most of the cases.

The therapeutic successes shown with the targeted therapy have not been evaluated in Mexico, for this reason, the present study is aimed to report the experience in a highly specialized oncology center in the systemic management of the GIST from the introduction of the TKIs.

Methods

Patients and study design

This is a retrospective, descriptive study of adult patients with the histological diagnosis of GIST, and positive immunohistochemical staining for CD117, with non-resectable or metastatic disease by extension studies and/or surgical exploration, treated with TKIs at the Oncology Hospital of National Medical Center for the Mexican Institute of Social Security.

We gathered the information of patients treated since

January 1st, 2007 to March 31st, 2014.

Methods

The demographic data, histopathological characteristics, as well as the documentation of the treatment initiation dates and the clinical evolution of the patients were obtained from the electronic files.

The radiological evaluation was performed within the internal system of imaging corroborating the response through the interpretation of the control images by radiology and imaging service.

The biochemical and laboratory documentation was obtained from the internal results report.

Safety and efficacy assessment

The primary efficacy endpoint was the treatment impact on the overall survival, defined by the time from the treatment initiation until the death of the patient. The secondary endpoints were the response rates, defined in accordance with the RECIST criteria, as well as the duration of response, and additionally, the time to the recurrence in the patients who submitted to a radical primary management.

The safety and tolerability assessment was documented for all patients treated with TKIs. The adverse events were classified based on the Common Toxicity Criteria of the National Institutes of Cancer.

Statistical analysis

The efficacy analyses were performed in patients who received at least 1 dose of the TKI. The population analyses were evaluated through descriptive statistics. The response rates were established via Pearson limits with a confidence interval of 95%. The time analyses were carried out using the Kaplan-Meier and Log-rank methods. The analysis of the information was done using the software SPSS v22.0.

Results

For the period evaluated, 71 GIST cases were documented, out of which 29 (40.8%) were men and 42 (59.2%) women. The overall median age was 59 years. The median age adjusted by gender showed a median of 57 for men (95% CI, 50.4–63.5) years compared with women who showed a median age of 58 (95% CI, 53–62) years, $P=0.767$.

At the moment of the diagnosis the performance status

Table 1 Demographic characteristics

Parameter	Men	Women	P value
Patients	29	42	0.051
Age (median) (years)	57	58	0.767
ECOG			0.891
0	2	2	
1	22	33	
2	5	7	
Primary site			0.812
Gastric	14	20	
Duodenum	7	9	
Jejunum	5	5	
Ileum	0	1	
Other	3	7	
Symptoms at diagnosis			0.948
Hemorrhage	9	10	
Pain	12	17	
Weight loss	4	8	
Occlusion	3	5	
Other	1	2	
Disease at treatment initiation			0.046
Metastatic	18	15	
Non-resectable	5	7	
Recurrent	6	20	
Involved sites			0.177
Liver	18	18	
Lung	4	3	
Retroperitoneum	4	12	
Other	3	9	

was distributed as follows: 5.6% had ECOG 0, 77.5% ECOG 1, and 16.9% ECOG 2 ($P<0.001$).

For the patients who were symptomatic at the diagnosis, the main symptoms were: upper gastrointestinal bleeding in 26%, abdominal pain 40.8%, weight loss 16.9%, bowel occlusion in 11.3%, and other symptoms in 4.2% ($P=0.06$).

The stages of the disease at the diagnosis were: metastatic in 46.5%, non-resectable in 16.9%, and recurrent in 36.6% ($P=0.03$). In the case of advanced disease, the main affected sites were: liver in 50.7%, lung in 9.9%, retroperitoneum in 22.5%, and other sites in 16.9% ($P=0.04$). The demographic parameters adjusted by gender are presented in *Table 1*.

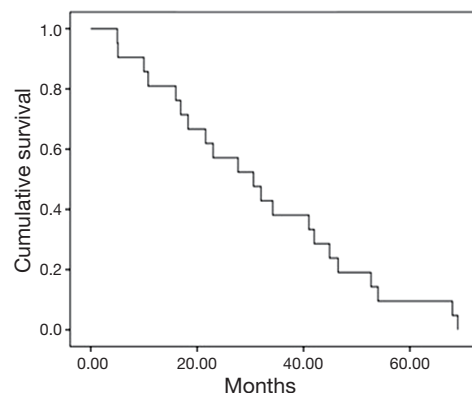
All the patients started with systemic management with imatinib a doses de 400 mg/d with a median interval of

Table 2 Response obtained with the initial systemic management ($P<0.001$)

Response	Frequency	%
CR	7	9.9
PR	13	18.3
SD	29	40.8
PD	22	31.0
Total	71	100.0

All responses differed significantly between the group ($P<0.001$)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

**Figure 1** Progression free survival in months in the overall group.

2 months (95% CI, 0.3–33.0).

Within the assessment of the response to the primary treatment, the stabilization of the disease was documented in 29 cases, followed by a partial response in 13, and complete response in 7 cases. Twenty two patients experienced progression with the initial management, showing a control disease rate of 49% ($P<0.001$) (*Table 2*).

Progression free survival

In general, the median progression free survival was 30.6 months (95% CI, 17.1–44.0) (*Figure 1*). Depending on the type of disease at the diagnosis, the median time to progression was 16.9 months for the metastatic disease (95% CI, 13.42–50.77), in the case of non-resectable disease the median time to progression was 23 months (95% CI, 7.1–35.31), while in the case of relapse of the disease the median time to progression was 30.6 months (95% CI, 20.5–40.6).

According with the extraintestinal site affected, the median progression free survivals in the study were: hepatic involvement, 34.2 months; pulmonary involvement,

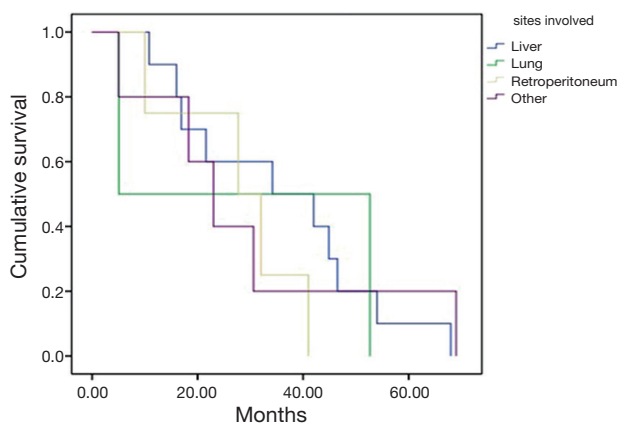


Figure 2 Progression free survival in months according with the extraintestinal site affected.

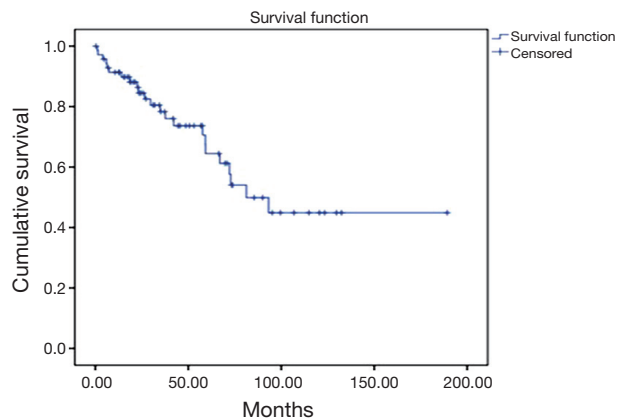


Figure 3 Overall survival of patients with advanced gastrointestinal stromal tumors (GIST).

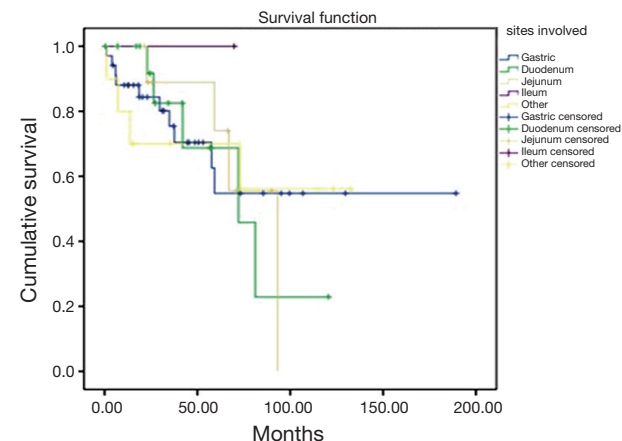


Figure 4 Overall survival of gastrointestinal stromal tumors (GIST) patients by involvement of primary site.

Table 3 Median and standard deviations observed in hematologic and biochemical parameters

Parameter	Median	95% CI	P
Leukocytes (mm ³)	5,600×	-0.6083-0.9826	0.64
Neutrophils (mm ³)	3,300×	-1.54-0.23	0.14
Hemoglobin (g/dL)	12.6	-0.60-0.75	0.82
Platelets (mm ³)	225,000×	-4.42-35.79	0.69
Creatinine (mg/dL)	0.99	-6.89-4.52	0.68
Total bilirubin (mg/dL)	0.56	-5.49-0.221	0.36
Alkaline phosphatase (mg/dL)	90	-40.35-14.15	0.30
LDH (mg/dL)	220	-23.45-30.12	0.64
AST (mg/dL)	45	-2.35-7.87	0.27
ALT (mg/dL)	21	0.67-11.40	0.80

LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine aminotransferase.

5.1 months; retroperitoneal, 27.7 months; and other sites, 30.6 months (Figure 2).

Overall survival

During the follow up, there were 23 deaths, showing a median estimated survival of 81.3 months (95% CI, 53.5-109) (Figure 3). A significant difference in the overall survival according with the affected site was observed, showing a median survival of 45 months for the patients with liver involvement, 25.7 months with pulmonary involvement, 36.2 months for the patients with retroperitoneal activity, and 37 months for those who presented activity in other sites (P=0.04) (Figure 4).

Toxicity

In relation to the hematologic toxicity, no statistical difference was observed in the blood counts for leukocytes, neutrophils, hemoglobin and platelets, independently of the evaluated cycle. Biochemically, there were no significant modifications observed in the follow up during the treatment (Table 3).

The clinical toxicity did not show relation with the administered doses, ruling out the secondary toxicity due to the cumulative doses. The observed tolerance was satisfactory and manageable in most cases, it is worth mentioning that there were 3 drug related deaths; one case due to fluid retention secondary to renal failure, and two cases in which they reported death out of the hospital, but

Table 4 Clinical toxicity observed during the tyrosine kinase inhibitors (TKIs) management

Toxicity	G0	G1	G2	G3	G4	G5
Diarrhea (%)	40	40	13.8	6.2	0	0
Fluid retention (%)	17.2	42.2	35.9	3.1	0	1.6
Fatigue (%)	20.3	46.9	21.9	6.3	4.7	0
Other (%)	61.3	0	25.8	0	9.7	3.2

Table 5 Updated status of patients in the last cohort evaluation

Status at last evaluation	%
Alive without disease	7.0
Alive with disease	54.9
Death	32.4
Lost to FU	5.6

related to infectious complications (*Table 4*).

According with the clinical evaluation, the status of the patients showed a statistically significant difference in favor of the patients alive with disease, followed by death patients; followed by the group of patients with complete response and a minority group represented by patients lost to follow up ($P=0.03$) (*Table 5*).

In relation with the last treatment administered to the patient, we can observe the management continuity based on imatinib 400 mg/d, represented in 72% of the cases ($P=0.002$), while the dose of 800 mg/d was administered to 14.1%, sunitinib in 9.8%, and other drugs 3.3%.

Discussion

The treatment of the gastrointestinal tumors has represented a dramatic evolution in the concept of the management of the metastatic, recurrent and/or non-resectable disease, with a transition from the cytotoxic therapy which offered modest response rates, to the initiation of the molecular targeted therapy for the inhibition of the enzymatic function of the BCR-ABL oncoprotein, presented in the studies by Druker and colleagues (4). Nowadays, the targeted therapies have demonstrated activity *in vivo* through the immune modulation, potentializing the antitumoral response through an increase of the T cells activity (5).

The demographic data obtained from our population showed a trend towards females, which contrasts with the published data, where there is a men:women ratio of 1–1.5:1,

in comparison, we observed in our study an turn around in the mentioned ratio. In relation with the age group, the median reported in European series is 66–69 years (6,7), and by the SEER (63 years) (8). The results show a median ten years lower for the age at the diagnosis, a very relevant figure for the cases in the Mexican population.

The relation of the sites affected with advanced disease correlates with data reported from international series, with a preponderance of hepatic activity, followed by lung, and retroperitoneal involvement in third place.

The clinical information comes from the results shown by Joensuu and colleagues, where a prolonged clinical response was documented with times surpassing 24 months in patients treated with imatinib (9). The tumor response rates in GIST patients, treated with imatinib reported in the trials by van Oosterom, Demetri, Verweij and Blanke (9-14) show as main treatment response stable disease with ranges of 45% to 56%; with complete response rates of 2% to 5%, and partial response of 20%, which translate into a clinical benefit of 70% to 90%, independently of the dose of 400, 600 or 800 mg/d. The results obtained in our site with imatinib doses of 400 mg/d show a complete response rate of 10%, partial response of 18%, and stable disease in 40% of the cases, reflecting a 70% clinical benefit, with similar rates to those reported in the series previously cited.

With respect to the overall survival, the study with the longest follow up (71 months), published by Blanke and colleagues (15) reports a median of 57 months, independently of the imatinib dose administered, in comparison, the series presented show a superior survival, with an estimated median of 81 months. It is worth mentioning that the difference may be influenced by the modifications made to the doses and regimens in case of progression, unlike the above mentioned study where the drug response is specifically evaluated to a pre-established dose. Additionally, it is necessary to consider the tumor biology that conditions a higher sensitivity to the treatment with TKIs, this warrants the need for the molecular evaluation of the tumors in patients treated at our hospital.

Unlike the existing information, in our study, we performed a subanalysis of the patients who died from the disease in correlation with the sites of primary involvement. It was possible to show a decrease in the survival in the cases with pulmonary involvement versus the hepatic, retroperitoneal, and other sites activity ($P=0.04$), establishing the pulmonary metastasis as a factor of poor prognosis in advanced GIST.

Conclusions

This study represents one of the most important reviews of the GIST in Mexico. It documents different and relevant conditions in the diagnosis and response to treatment, to those documented in international series. A higher tumor response is observed with the subsequent impact on the overall survival. This study sets the bases to initiate studies at the molecular level aimed to determine biological differences that justify the clinical behavior, characteristics of our group cases.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The trial was approved by the institutional review board or ethics committee at each center and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent.

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