Gastrointestinal stromal tumors (GIST): Factors predictive of survival after R0-cytoreduction


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RESUMEN

Objetivo: analizar los posibles factores pronósticos de supervivencia en tumores estromales gastrointestinales c-kit positivo (GIST), tras citoreducción óptima R0.

Pacientes y método: estudio de 35 pacientes intervenidos en nuestra Unidad desde enero 2002 a febrero 2007, con tumores del estroma gastrointestinal CD117/c-kit positivo en los que se alcanzó citoreducción quirúrgica sin residuo tumoral macroscópico. Una base de datos prospectiva nos proporcionó las distintas variables analizadas, de carácter demográfico, anatómico, clínico, histopatológico e inmunohistoquímico, entre otras. El análisis de la supervivencia actuarial se realizó según el método de Kaplan-Meier y el análisis multivariante mediante el método de regresión múltiple de Cox.

Resultados: la supervivencia global a 5 años fue del 77%, con una supervivencia media de 52 meses. El riesgo de malignidad según la clasificación de Fletcher y el tamaño tumoral mayor de 10 cm, influyeron significativamente de forma negativa sobre la supervivencia de los pacientes, tras el análisis univariante realizado (p < 0,05). La actividad proliferativa Ki-67 mayor del 50% fue la única covariable con significación estadística en el análisis multivariante. El 20% de los tumores recayeron. Sólo 3 pacientes metastásicos recibieron tratamiento adyuvante con mesilato de imatinib, todos ellos con Ki-67 > 50% y vivos en la actualidad.

Conclusiones: el índice proliferativo Ki-67 podría representar un excelente marcador pronóstico de supervivencia en aquellos pacientes con tumores del estroma gastrointestinal c-kit positivo. Su confirmación y el punto de corte adecuado deberían ser objeto de futuros estudios prospectivos, así como su posible utilidad para seleccionar pacientes candidatos al tratamiento con mesilato de imatinib.

Palabras clave: GIST. c-kit. Neoplasia mesenquimal.

ABSTRACT

Objective: to analyze the different factors predictive of survival associated with optimal R0-cytoreduction in c-kit-positive gastrointestinal stromal tumors.

Methods: thirty-five patients were operated on in our Oncological Surgery Department from January 2002 to February 2007 because of CD117/c-kit-positive gastrointestinal stromal tumors, and an optimal surgical cytoreduction was obtained without macroscopical residual disease. Demographic, anatomical, clinical, pathological, and immunohistochemical variables were analyzed from a specific database. Survival and multivariate analyses were developed using Kaplan-Meier and multiple Cox regression models, respectively.

Results: five-year overall survival was 77% with a mean survival of 52 months. Risk of malignant behaviour according to Fletcher’s classification and tumor size higher than 10 cm had a significantly negative influence on overall survival in the univariate analysis (p < 0.05). Proliferative Ki-67 activity higher than 50% was the only statistically significant variable in the multivariate analysis. Twenty percent of tumors recurred. Only 3 patients with metastatic disease received adjuvant treatment with imatinib mesylate, all of them with Ki-67 > 50% and currently alive.

Conclusions: the proliferative Ki-67 index could represent an excellent predictive factor for survival in patients with c-kit-positive stromal gastrointestinal tumors. Confirmation and an adequate cut-off level should be the main objectives for future prospective studies, mostly focused on the appropriate selection of optimal candidates to imatinib-mesylate-based treatment.

Key words: GIST. c-kit. Mesenchymal tumor.
INTRODUCTION

Since 1983 the term GIST (Gastrointestinal Stromal Tumors) defines a subgroup of tumors from the gastrointestinal mesenchyma that show no muscular or neural differentiation, and that represent 2% of all tumors in the gastrointestinal tract (1).

When the c-kit gene was first described, GISTs were supposed to arise from interstitial Cajal-like cells, because they share a common positivity to this gene.

The classification according to prognostic factors and malignancy risk, as well as the application of imatinib mesylate (c-kit tyrosin-kinase inhibitor), have progressively increased interest in these tumours.

A research line is based on identifying prognostic factors that could affect survival in these patients. In that sense, in contrast to the classical factors described by Fletcher (2), including size and mitotic index, there have recently appeared other factors such as the Ki-67 cellular proliferative index, whose prognostic implication is still controversial. The aim of the present study is to analyze the outcome, morbidity, and mortality of patients operated on in our Unit of Surgical Oncology for GIST tumors where an optimal R0-cytoreduction was achieved, mainly focusing on the potential factors predictive of survival in our series of patients.

PATIENTS AND METHODS

Patients

The present study included 35 patients with gastrointestinal stromal tumors (GIST) who underwent a surgical procedure at Unit of Surgical Oncology, University Hospital Reina Sofía, from January 2002 to February 2007, with a follow-up period ending in June 2007. Data were included in a prospective database.

Inclusion criteria included: a) tumors with histopathological origin in the gastrointestinal stroma; b) positivity to immunohistochemical marker CD117 or c-kit; c) R0 oncological resection criteria (no macroscopic residual tumor); d) absence of other known associated malignant neoplasms; and e) Karnofsky performance status index > 70%.

Variables included in our study were: age, gender, anatomical gastrointestinal origin, presence or absence of symptoms, metastases, size (≤ 2 cm, 2-5 cm, 5-10 cm, > 10 cm), histological subtype (fusocellular, epithelioid, mixed), mitotic index (number of mitoses per 50 high-power fields: ≤ 5 m/50 CGA, 5-10 m/50 CGA, > 10 m/50 CGA), potential risk of malignancy, cellular atypia (absent, mild, moderate, severe), presence or absence of necrosis, tumor hemorrhage or ulceration, immunohistochemical markers (CD34, smooth muscle actin –SMA–, vimentin, neuron-specific enolase –NSE–, glycoprotein S-100, desmin, Ki-67 proliferative index), postoperative stay, surgical morbidity and mortality, tumor recurrence, treatment with imatinib, and outcome.

Tumor tissues were fixed in 10% neutral formal. The formal-fixed tissue was embedded in paraffin. Histological sections obtained from formaline-fixed and paraffin-embedded tissue were deparaffinized in xilol and stained with hematoxylin-eosin for further evaluation. Tumors were classified in groups according to Fletcher’s risk assessment system supported by National Institute of Health (NIH) consensus risk categories: very low-, low-, intermediate-, and high-risk.

Immunohistochemical assessment

All tumor samples were examined for various markers using commercially available immunohistochemical antibodies against CD 117-cKit (A4502, polyclonal, Dako, USA; 1:50 dilution), CD34 (clone QBEnd/10, Novocastra Labs; 1:50), SMA (clone asm-1. Dako; 1:200), NSE (clone 5E2: Novocstra Labs; 1:100), S-100 (clone S1/61/69. Novocastra Labs; 1:50), desmin (clone DE-R-11. Novocastra Labs; 1:100).

Ki-67 proliferative index (clone MIB-1, 1:25 dilution) was determined by the standard procedure: MIB-1 score as the ratio of the positive-stained nuclei to the total number of tumor cells by examining 400 high-power fields in representative areas with 1,000 cells. Thus, a proliferative activity classification was performed as: low proliferative activity when the percentage was under 10%; moderate proliferative activity when it was between 10 and 50%; and high proliferative activity when it was over 50%.

Statistical analysis

SPSS 11.0 for Windows (Microsoft®, USA) was the program used for the statistical analysis. Mean and proportion differences were obtained by the application of the Chi squared, Student’s t, and variance analyses. Survival and multivariate analyses were developed using the Kaplan-Meier test and Cox regression model, respectively. In every test a confidence interval of 95% or a p value under 0.05 was considered statistically significant.

RESULTS

Descriptive results

During the study period 1,720 digestive tumors were diagnosed in Hospital Reina Sofía, 38 of which were GISTs. Thirty-five patients show selection criteria and were included in the study. Three patients were excluded, 2 of them because of concomitant malignant neoplasms and 1 patient because of a Karnofsky performance status index below 70%. Mean presentation age
was 60 years (range: 25-84); most cases developed between age 60 to 70 years; 54% were women and 46% were men. Most common anatomical locations were the stomach (48%) and small bowel (46%), followed by the mesentery (6%); 86% of patients had symptoms, mainly upper digestive bleeding, constitutional syndrome, anemia and abdominal pain. Twenty-three percent of patients had metastatic disease, half in the liver and half in the peritoneum (Table I).

Mean tumor size was 9.4 cm, with a median of 8 cm (range: 2-33). Sixty percent of patients had a tumor size over 5 cm, and 29% over 10 cm. In nearly half of patients a mixed cell strain (fusocellular-epithelioid) was most frequent; 29 and 23%, respectively, had an epithelioid and a fusocellular tumor type. Hemorrhage, necrosis, and ulceration were seen in 37, 34, and 11% of patients, respectively.

The mitotic index was under 5 mitoses/50 HPF in 66% of patients, of 6-10 mitoses/50 HPF in 11%, and higher than 10 mitoses/50 HPF in 23%. Cellular atypia was seen in 43% of patients; 23% had relevant levels of it. Resected tumors showed the following proportions according to their malignancy risk: very low risk 0%, low risk 34%, intermediate risk 23%, high risk 20%, and malignant 23%.

An immunohistochemical study for CD117 was positive in 100% of patients (inclusion criteria). The following markers appeared in the following proportions: CD34 (69%), smooth muscle actin (46%), vimentin (6%), neuron-specific enolase (6%), glycoprotein S-100 (3%), and desmin (3%). Ki-67 proliferative activity index was > 10 in 46%, 10-50 in 31%, and > 50 in 23% of patients.

Median postoperative stay was 8 days, with a range from 4 to 26 days. Postoperative morbidity was 14% because of two intraabdominal abscesses, one atelectasis, one case of pneumonia, and one case of wound infection. No surgical mortality was recorded for this cohort of patients. Only 3 patients (9%) received imatinib mesylate, all of them with a proliferative activity index > 50%, and considered malignant because of the presence of metastases. These three patients received this drug as part of an adjuvant chemotherapy protocol, and were alive and free of recurrence at the end of this study. Local or distant recurrence occurred in 7 patients (20%); all of these tumors were classified as high-risk or malignant according to Fletcher’s classification.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Mitoses (≥50 HPF)</th>
<th>Ki-67 (%)</th>
<th>Metastasis Site</th>
<th>Surgery</th>
<th>Treatment</th>
<th>Survival Data/months</th>
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<td>&gt; 10/50</td>
<td>&gt; 50</td>
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<td>M</td>
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<td>&gt; 10/50</td>
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<td>Alive (9)</td>
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Survival results

Overall survival at 3 and 5 years, according to Kaplan-Meier test, was 83 and 77%, respectively, with a median survival of 52 months. There were no statistically significant differences at 5 years in sex (89% for women vs. 70% for men, \( p = 0.50 \)) or anatomical gastric or small-bowel location (67 vs. 86%, respectively, \( p = 0.34 \)). In this sense there were no statistically significant differences in the presence or absence of symptoms on overall 5-year survival (77 vs. 75%, \( p = 0.88 \)).

The presence of synchronic metastases, although resectable, had an important influence on 5-year survival but was not statistically significant (47 vs. 87%, \( p = 0.05 \)). Something similar happened when survival was analyzed according to mitotic index with a cut-off point of 10 mitosis per 50 high-power-fields: 5-year overall survival was 87% for \( \leq 10/50 \) HPF with a mean survival of 53 months, versus 47% for \( >10/50 \) HPF and a mean survival of 41 months (Fig. 1).

Local or distant recurrence of GIST had a positive but not statistically significant association with poorer survival. Thus, patients with tumor recurrence had a 5-year survival of 33 against 88% in those without recurrence (\( p = 0.06 \)). Most of these patients underwent a reoperation (4/7).

The association of very low, low, and intermediate risk of Fletcher’s classification against the high-risk and malignant groups showed statistically significant differences (95 vs. 54%, respectively) (Fig. 2). Tumor size was also a variable which had influence on 5-year survival. When the cut-off point was established at 10 cm, patients with tumors under 10 cm had a statistically significant better survival when compared to those who had tumors greater than 10 cm (91 vs. 31%, respectively, \( p = 0.01 \)), with an overall mean survival of 54 months against 37 (Fig. 3).

All immunohistochemical markers but CD34 and SMA had no statistically significant influence on survival. Ki-67 showed a statistically significant influence on survival when the proliferative activity index cut-off point was Ki-67 < 50% vs. Ki-67 > 50% (92 vs. 23%, respectively, \( p = 0.001 \)) (Fig. 4). This covariable was the only one that had a statistically significant association in the multivariate analysis by the Cox proportional regression model (\( B = 1.976; \text{Wald} = 3.718; p = 0.045 \); Odds ratio = 7.214; 95% CI = 0.968-53.765). In this sense, a Ki-67 proliferative activity index \( \leq 50\% \) has been the only survival predictor covariable in our cohort of patients with GIST undergoing a surgical R0 cytoreductive procedure.
DISCUSSION

One of the main problems when studying gastrointestinal stromal tumors is their low incidence. Strong CD117 positivity and also variable CD34 positivity, as well as its gastrointestinal origin, is what confirms a GIST but not a leiomyoma or leiomyosarcoma (3).

In our series of patients, results about age and gender coincide with previous reports, mainly showing a low incidence before 40 years of age (4), as well as no difference in gender distribution (5). Clinical presentation did not differ from other groups, with a higher incidence of symptomatic patients with gastrointestinal bleeding, abdominal pain or palpation of abdominal mass against incidental cases (6,7). It is known that GIST distribution shows no differences between gastric and small-bowel origin (8), and although some studies report a better prognosis for GISTs of gastric origin with the same size and number of mitoses (5,9), we have not found any significant difference between groups. Thus, in our series the predominating group was the fusocellular-epithelioid histological subtype, without any influence on overall outcome.

Based on our results, the liver and peritoneum are the main locations for metastases (10). In this sense, and as other groups have previously reported, neither necrosis, nor ulceration or hemorrhage are related with a higher malignancy risk (9,11), and as Miettinen described, cellular atypia has no significant relationship with survival and malignancy risk (9).

Our patients have a similar distribution of immunohistochemical markers when compared to previously reported cases, with CD34, smooth-muscle actin and mainly CD117 being the most common ones for GIST (12,13).

A 5-year overall survival over 75% for patients with optimal oncological resection (R0) coincides in our series with that reported by other authors (14-16). Recurrence and median survival of recurrent resected R0 tumors in our series shows better results than previously reported by other groups —40% at 2-years (17). Our median survival of 37 months can be explained because 5 of the 7 recurrence cases present in our study were potentially resectable. This second resection makes mean survival increase around 12 to 18 months, as Bonvalot reported (18).

The importance of the mitotic index as a prognostic factor has been widely described, mainly when it is higher than 10 mitoses per 50 HPF (19,20). We found no statistically significant relationship between mitotic index and survival (p = 0.05), although we think that an increase in number of patients would be enough to make this test reach statistical significance.

Tumor size was widespread in our series of patients from 1 to 30 cm with a median of 8 cm. A cut-off point in 10 cm implies a significant difference in the prognosis of these patients: 90 vs. 30% 5-year overall survival in our series as well as in other series, including that by Orosz (11).

The Ki-67 proliferative index has been included as a poor prognostic factor for GIST, as has been the mitotic index, but this still remains controversial according to previous reports (21-24). This may probably be the main contribution of our study. In this sense, a Ki-67 > 50% was a poor prognostic factor for overall survival both in univariate (p = 0.001) and multivariate analyses (p < 0.1). These data coincide with previous reports such as those by Ozguc (3), where a Ki-67 proliferative index > 82% appeared as a survival prognostic factor. Nevertheless, further prospective studies will set the correct cut-off point for the Ki-67 proliferative index percentage, which has different values in some reports (10).

In conclusion, at present we can only state that surgery is the only potentially curative procedure for GIST. An optimal surgical R0 procedure should take precedence over functional resection. Thus, potentially resectable recurrences must be removed, as lower recurrence and better survival rates are reported. The use of imatinib mesylate must be linked to tumor resectability (25), either with adjuvant, neoadjuvant, or palliative intent, which are the primary endpoints of most current multicenter clinical trials. The inclusion of Ki-67 in prospective multicenter
studies, and its relationship with other risk indexes such as Fletcher’s mitotic index, could better establish the risk of malignantancy and recurrence for these tumors, as well as which patients are candidates for adjuvant or neoadjuvant therapies with imatinib mesylate.

REFERENCES