Short Communication

Gastrointestinal stromal tumors in the imatinib era: 15 years' experience of a tertiary center

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Abstract: Gastrointestinal stromal tumors (GISTs) were associated with a disease free survival rate of disease of 50% at 5 years, but the actual natural history since the advent of imatinib is poorly described. Our objective was to evaluate the evolution in the treatment and prognosis of patients with GISTs since the start of imatinib. Retrospective analysis of GISTs diagnosed between January 2000 and June 2015 in a Portuguese large volume center. We included 131 patients, 55% female, with a mean age of 64±14 years, followed for a median of 30 months; 64% of cases had gastric involvement; 92% of the tumors were c-Kit positive; 95% of patients were operated. Imatinib was initiated in 25% of patients, as adjuvant therapy in 69%; 75% reported adverse effects, and 16% developed resistance. The recurrence rate was 4%, and was associated with age at diagnosis (P=0.037), tumor size (P=0.028), presence of metastases (P=0.019) and high-risk lesions (P=0.036). Survival at 1, 3 and 5 years was 87%, 71% and 61%, respectively. One year's mortality was significantly associated with tumor size (P=0.021), stage IV at diagnosis (P=0.003), non-complete resection (P=0.002) and palliation with imatinib (P=0.035). Similar associations were observed at the 3 and 5 years. In the imatinib era there is an increased long-term survival in comparison with previous epidemiological data, and reduced recurrence rates. In more advanced cases survival remains limited in the short term.

Keywords: Gastrointestinal stromal tumors (GISTs); imatinib; prognosis

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal mesenchymal tumor, which accounts for 0.2% of all gastrointestinal tumors (1). GISTs, are defined as pleomorphic mesenchymal tumors of the gastrointestinal tract that express the KIT protein CD117 and often also CD34 on immunohistochemistry (IHC) (2). Tumor size, mitotic rate and tumor site are considered as the most important prognostic parameters for patients after surgery (3). Complete resection, together with tumor-free margins and avoidance of tumor rupture, remain the best option for a curative approach for resectable GISTs. Unfortunately, approximately two thirds of patients with GISTs will experience recurrence or metastasis during the course of their disease (4). The post-operation outcome of GIST is highly variable, with 5-year survival rate ranging from 48% to 80%, which is mainly due to the introduction of a tyrosine kinases inhibitor (TKI), imatinib mesylate, which was used in metastatic/recurrent GISTs since 2000 (3,4,5). As so, the current natural history of the disease is not completely characterized.

In order to understand the behavior of this condition in the post-imatinib we decided to make a retrospective evaluation of patients with GISTs diagnosed since 2000 in our tertiary center.

Methods

The study was performed in patients operated between 2000 and 2015, in whom pathological diagnosis of GIST was established. The diagnosis was grounded following elements of clinical, imaging and morphological diagnosis (macroscopic, histological and IHC), on which was established the indication for surgery and adjuvant therapy.

Only the cases with complete medical records and pathological data were involved in present study. The following parameters were reviewed and analyzed: age, sex, clinical presentation, surgical detail, tumor site, tumor size, mitotic rate, IHC [CD117, CD34, vimentin, smooth muscle actin (SMA), S-100, discovered on GIST 1 (DOG1)], TKI therapy and outcome.

Location of the GIST, size of the tumor, degree of differentiation, and lymph node metastasis were assessed according to the pTNM classification and the modified National Institutes of Health (NIH) consensus classification system (6). Patients who underwent curative surgical treatment for this study were divided into two groups based on the modified NIH consensus classification system: those with high-risk GISTs (high-risk group) and those with very low-, low-, and intermediate-risk GISTs (lower-risk group).

Primary outcomes included 1-year, 3-year, and 5-year survival (overall and tumor-free). Secondary outcomes were recurrence of the disease and time to recurrence. For each of the outcomes, risk factors were assessed.

Data were analyzed using SPSS version 21.0. Quantitative data were presented as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Overall survival was calculated from the date of pathological diagnosis to date of death or last follow up. Disease free survival was calculated from date of surgical intervention to date of recurrence or death or last follow up. The chi-square test was used to analyze the possible relationships between the clinical and pathological features, considering P values of <0.05 statistically significant.

Results

Since 2000 we identified 131 patients diagnosed with GIST. The gender distribution was similar (55% female, 45% male). The mean age at diagnosis was 64±14 years, and the patients were followed for a median period of 30 months [interquartile range (IQR): 11–68 months]. Four patients had history of previous GISTs in first degree relatives. Most patients were symptomatic at diagnosis (56.5%). The main symptoms included gastrointestinal bleeding (38.4%), abdominal pain (30.1%), and weight loss (9.8%). Of note, nearly half of the patients presented with some degree of anemia (48.1%).

The lesions were identified in 45% of cases by endoscopic studies, mainly upper endoscopy, and in 32.1% by CT scan or MRI. Interestingly, in 26 patients (19.8%), the lesions were identified after surgical specimens' analysis of surgeries performed for other reasons. Twenty-eight patients were assessed by endoscopic ultrasonography, and in 45% of cases cytology was performed (all in the stomach), with a diagnostic accuracy of 54%.

As expected, the stomach was the most frequently involved organ in 64.1% of cases, with the lesions being distributed through the fundus (15.5%), body (61.9%) and antrum (22.6%). The small bowel was involved in 29.8% of cases, with a similar distribution between the duodenum, jejunum and ileum (30.8%, 30.8% and 38.5%, respectively). Less frequently, the primary lesion was located in the colon (3.8%, all of the left colon or rectum) or in the esophagus (three cases, 2.3%). The average tumor size was 56±44 mm, with 17.1% of the cases measuring less than 20 mm, and 10.6% by measuring more than 100 mm. In the 38 patients (29%), the tumor involved adjacent structures, however, only 8.4% had involvement of loco-regional lymph nodes. Sixteen patients (12.2%) had metastatic disease with 80% of metastases located in the liver. Using the TNM classification, 55% were in stage I, 15.3% in stage II, 15.3% in stage III and 14.5% in stage IV.

Nonetheless, 94.7% of patients underwent surgery (n=124), including curative resection and palliative resection. Regarding the identified histologic types, the vast majority of patients had tumors with fusiform cells (70.2%), while in 10.7% of cases the tumors were of epithelioid type. Immunohistochemical studies revealed positive for c-KIT in 92.2% of cases, while the search for of CD34 was positive in 63.7%. Less often have identified the presence of DOG1 (25%), SMA (16%), desmin (13.3%) and S100 (10.2%). The mitotic index shows usually little aggressive behavior, with index <5 mitoses/HPF in 75.9% of cases, and >10 mitoses/HPF in only 9.5%. According to the NIH risk classification, the tumors were classified as follows: very low in 17.8%, low in 28.8%, intermediate in 25.4% and high in 28%.

Approximately a quarter of the patients started treatment with imatinib (24.8%), which in 69% of cases was used as adjunctive therapy, and less frequently as a palliative agent. Of note, 75% of patients experienced adverse effects, the most common edema in 21.9%, nausea, fatigue and diarrhea (each of them in 9.4%). Potentially serious complications

were rare, notably hepatotoxicity and neutropenia (both 3.1%). However, only three patients (9.4%) discontinued the medication for adverse effects. The imatinib resistance rate was 15.6% (five patients), treated with dose increasing in three cases (60%).

Resistance was associated with presence of lymph node involvement (P=0.025) and positive IHC for DOG-1 (P=0.017). The recurrence rate after "curative" surgery was 4%, and was associated with age at diagnosis (78 *vs.* 64 years, P=0.037), tumor size (124 *vs.* 53 mm, P=0.028), presence of metastases (16.7% *vs.* 2.7%, P=0.019), and high-risk lesions (13.3% *vs.* 5%, P=0.036).

Survival at 1, 3 and 5 years was 87%, 71% and 61%, respectively. One year's mortality was significantly associated with tumor size (87.5% if <20 mm *vs.* 58.3% if >10 mm, P=0.021), stage IV at diagnosis (89.9% in stage I *vs.* 58.8 in stage IV, P=0.003), non-complete resection (61.5% *vs.* 91.5%, P=0.002) and palliation with imatinib (66.7% *vs.* 95.2%, P=0.035).

The survival rate at 3 years was related to the presence of local invasion (55.2% *vs.* 80.9%, P=0.016), involvement of loco-regional lymph nodes (25% *vs.* 76.5%, P=0.002), presence of metastases in other organs (36.4% *vs.* 76.9%, P=0.006), stage IV at diagnosis (30.8% *vs.* 80%, P=0.006), positive for DOG1 (0 *vs.* 77.1%, P=0.005), and surgical approach (73.6% *vs.* 25%, P=0.037). Although not statistically significant, there was a trend in the 3-year survival in patients receiving imatinib as adjuvant treatment compared to palliative treatment (81.8% *vs.* 42.9%, P=0.087).

The 5-year survival was related to lesion size >10 cm (58.3% *vs.* 58.3%, P=0.021), presence of local invasion (70.6% *vs.* 93.6%, P=0.001), loco-regional lymph nodes invasion (45.5% *vs.* 91.1%, P<0.001), metastases in other organs (64.3% *vs.* 89.9%, P=0.009) and stage IV at diagnosis (58.8% *vs.* 92%, P=0.003). Although not reaching statistically significance, surgical approach showed a favorable trend in relation to the 5-year survival (87.9% *vs.* 60%, P=0.074), especially in R0 resections (91.5% *vs.* 61.5%, P=0.002). Again, the use of imatinib as adjunctive therapy was statistically related to the 5-year survival (95.2% *vs.* 66.7%, P=0.035). Also, at 5 years imatinib resistance development negatively influenced survival (60% *vs.* 92.0%, P=0.05).

Discussion

GISTs are the most common stromal/mesenchymal neoplasm affecting the gastrointestinal tract (7). Their particular molecular characteristics gives to this group of neoplasms a unique biologic activity.

In our series, the mean age (64±14 years) is similar to other data previous published in two European studies (8,9). In these series, one from in Sweden and other from Iceland, the mean age was 66 and 69 years, respectively. Four patients presented with family history of GIST (3.8%), and previous literature reports 5% of all GIST cases as family forms of disease, that can origin in neurofibromatosis type 1, Carney-Strakis syndrome or in primary familial GIST syndrome (10-12). In the clinical records consulted there was no reference to genetic diagnosis in patients with family history of disease. Such data should alert physicians to the prompt diagnosis of familiar syndromes, so that its prompt diagnosis could enable clinicians to early diagnosis of asymptomatic cases.

In our data, most patients had symptoms at the time of diagnosis (58%). The most commonly reported symptoms were pain, weight loss and digestive hemorrhage. Such symptoms are similar to data published in a 1996 Japanese series that analyzes the clinical presentation of stromal tumors (GIST and non-GIST) (13). DeMatteo *et al.* showed that GISTs are usually associated with non-specific symptoms (early satiety, abdominal discomfort), however similar symptoms to those we found in that series were associated with exuberant growth (3). This could be explained by the fact that our data correspond to a tertiary center where to where the most complex/advanced cases are referred and managed.

In about one in five cases (19.8%) the tumors were identified accidentally, through the anatomopathological analysis of surgical pieces obtained for other reasons. This allows us to conclude that subclinical GIST may be a pathology with a prevalence that is much higher than we expected. In a Japanese study, serial analysis of 100 pieces of gastrectomy (obtained in the context of gastric adenocarcinoma) revealed the presence of 50 microscopic GISTs (diagnosed by IHC) in 35 analyzed stomachs (14).

Regarding the immunohistochemical features, no doubt exists that c-KIT/CD117 is the corner stone of GIST diagnosis (7). Such a marker allows the differential diagnosis with other mesenchymal neoplasms, namely leiomyoma/leiomyosarcoma (15). In our patients, c-KIT was positive in 92% of the cases, what is somewhat higher than previous data that showed an 80% positivity for this marker (7). The CD117 molecule is a part of the c-KIT receptor, a tyrosine kinase originating in the KIT proto-oncogene. Therefore, the clinical response to imatinib is dependent on the tumor genotype: in a previous study of 127 cases of GIST, all

those who had a c-KIT mutation showed clinical response to imatinib; those with other alterations [e.g., mutation in platelet-derived growth factor receptor A (PDGFRA)] showed partial clinical response (16). However, the clinical response to imatinib is dependent on the type of c-KIT mutation. The mutation in exon 11 is more likely to respond than the mutation in exon 9 (17). Despite this, treatment with imatinib is recommended in all cases of c-KIT expression, regardless of the mutation presented (18,19). The usefulness of the drug in surgical and non-surgical candidates is widely described. It was found that after the introduction of imatinib in clinical practice, survival of patients with advanced GIST increased from 18 to 57 months (20).

We found positivity to DOG-1 (discovered on GIST-1) in 25% of our cases, which is a recently described protein expressed in GISTs irrespective of mutation status. Indeed, previous works identified DOG-1 as an universal marker of GIST (expressed inclusively in negative c-KIT cases) (21,22). Therefore, such prevalence may be due to the absence of an active search for this marker in the first years of our cohort, thus such information in lacking in histopathology reports. The fact that the multivariate analysis has identified the positivity of DOG-1 as a marker of resistance to imatinib and of a shorter survival at 3 years should be viewed with caution and may correspond to a bias.

In our analysis, there was no statistically significant difference in survival at 1 and 3 years with the use of imatinib. Although the biological response rate with imatinib is highly validated, clinical trials with this drug also showed no difference in survival. One reason for this lack of effect was due to the short follow-up period, the reduced number of disease recurrences, and the fact that all patients were included in the treatment arm after the occult phase of the clinical trial (20,23).

According to current guidelines, some clinical and histological features are associated with risk for recurrence of disease under therapy with imatinib. These factors are defined by the NIH consensus and Armed Forces Institute of Pathology (AFIP) criteria, which include tumor size, number of mitoses, non-gastric location, presence of rupture, and male gender (6,24,25). In our series, advanced age presented as a risk factor for recurrence, a risk not contemplated in current scores, and may improve the prediction of response to this drug if validated prospectively.

Conclusions

In conclusion, in this imatinib era of GIST management, there is an increased long-term survival in comparison with previous epidemiological data, and reduced recurrence rates. Performing surgery remains the best therapeutic option and should be the first choice whenever possible, bring that the use of imatinib has the most benefit when used as an adjuvant treatment, mainly in cases with lower tumor burden. In more advanced cases, survival remains limited in the short term despite imatinib use.

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None.

Footnote

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

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