ABCDDV/1103

ABCD Arq Bras Cir Dig
2015;28(2):124-127
DOI:http://dx.doi.org/10.1590/S0102-67202015000200010

Original Article

PROFILE OF PATIENTS WITH GASTROINTESTINAL STROMAL TUMORS (GIST)

Perfil de pacientes portadores de tumores estromais gastrointestinais (GIST)

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ABSTRACT - *Background*: There is an improvement on the GIST treatment in last decade due to biomolecular research and adjuvant therapy with tyrosine kinases inibitors. However, both modalities of treatment rarely are available in Brazilian public hospital. ***Aim*:** Evaluate GIST patients profile in public oncologic hospital. ***Methods***: A retrospective study was made on patients with GIST diagnosed and treated between 2001 and 2013. ***Results*:** Sixty-nine patients were included, mean age 59 years with slight predominance in females (51%). The main symptom was abdominal pain associated with incidental imaging finding. The occurrence of other associated neoplasm was in 28.8% of cases. The positivity of CD117 was 97.1%. The most frequent location was the stomach in 55.1% of cases. The R0 resection was possible in 63.8% and the recurrence rate was 20.3 %, with liver and peritoneum the main affected sites. Overall survival in the whole sample was 71%. Free survival rate of disease was 64%. The use of imatinib was limited to patients with residual disease (unresectable disease, R2 and R1 resection), metastatic disease or recurrence. ***Conclusion*:** In order to improve GIST treatment is necessary to add the biomolecular analysis to risk stratification. However, for this to occur, incentive in biomolecular research is required, to increase the possibility of patient survival.

HEADINGS - Gastrointestinal stromal tumors. Survival rate. Risk factors. Surgery.

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Financial source: none
Conflicts of interest: none

Received for publication: 09/01/2015
Accepted for publication: 10/03/2015

RESUMO - *Racional*: O tratamento do GIST tem se aprimorado muito na última década através das pesquisas biomoleculares e o uso adjuvante dos inibidores das tirosinas quinases. Entretanto, nos hospitais públicos brasileiros nem sempre são disponíveis tais ferramentas. ***Objetivo*:** Avaliar o perfil dos pacientes portadores de GIST em hospital público oncológico. ***Métodos*:** Análise retrospectiva de todos os casos de GIST tratados no período de 2001 a 2013. ***Resultados*:** Analisaram-se 69 pacientes, com média de idade de 59 anos e com discreto predomínio no sexo feminino (51%). A principal forma de apresentação clínica foi dor abdominal associada com achado de exame de imagem. A ocorrência de outra neoplasia associada foi de 28,8%. A positividade do CD117 foi de 97,1%. A localização mais frequente foi o estômago em 55,1%. A ressecção R0 foi possível em 63,8% dos casos e a taxa de recidiva foi de 20,3%, sendo fígado e peritôneo os sítios principais acometidos. A sobrevida global na amostra toda foi de 71%. A taxa de sobrevida livre de doença foi de 64%. A utilização do imatinibe ficou restrita aos pacientes com doença residual (ressecção R2, R1 ou metastáticos), irressecáveis ou com recidiva. ***Conclusão*:** Afim de aprimorar o tratamento do GIST é necessário acrescentar a análise biomolecular à estratificação de risco. Porém, para que isto ocorra, políticas de incentivo e fomento na pesquisa biomolecular são necessárias, ampliando a possibilidade de sobrevida dos pacientes.

DESCRITORES - Tumores do estroma gastrointestinal. Taxa de sobrevida. Fatores de risco. Cirurgia.

INTRODUCTION

Among the cancers of the digestive tract, the stromal gastrointestinal tumors (connective tissue) have gained prominence within the clinical research. The precursor cells from these tumors are interstitial cells of Cajal, located in the wall of the gastrointestinal tract and make the connection with the smooth muscle to autonomic nerve plexus. Are pluripotent cells with neuronal characteristics such as smooth muscle cells being called "pacemaker" of peristalsis[15].

Historically, these tumors were studied since 1940 and for a long time were confused as sarcomas of smooth muscles[2]. The use of electron microscopy and the advent of immunohistochemical, the gastrointestinal stromal tumor was named GIST in 1983 by Mazur and Clark[17] and was ratified in 1998 with Kindblon[15] and Hirota[10] through the demonstration of the CD34 antigen (mesenchymal cell marker hematopoietic precursor) and CD117 (C-kit protein).

In the begining, the positivity for CD34 gave the title "GIST" myogenic and other neuronal tumors[21], while after the use of CD117, these tumors were removed from GIST diagnosis due to its negative CD117 .

The CD117 cell surface antigen is the extracellular portion of transmembrane protein tyrosine kinase which is the product of the KIT proto-oncogene. Thus, approximately 80 % of GISTs, the mutation in this gene leads to activation of protein and triggers hyperplasia cellular process[28] .

In 2001, the ACH started the immunohistochemical analysis for the detection of CD117 (C-kit) in order to diagnose cases of GIST and, so, include them in treatment protocols as disease staging. Thus, Amaral Carvalho Hospital has become a reference center for the treatment of this rare type of tumor.

Therefore, the objective of this study was to analyze the profile of patients treated and to identify possible gaps in treatment that can be improved.

METHODS

This research was approved by the Research Ethics Committee of the Institution (SISNEP/CONEP) under number 138/11.

A retrospective study of all cases of GIST diagnosed from 2001 to 2013 was done. After the survey, the medical records were analyzed and demographics, medical history, location and tumor size, immunohistochemical profile, mitosis number by 50 fields, associated malignancies and disease-free interval and overall survival. The risk stratification group guidelines followed were: NIH (National Institute of Health) modified by Joenssu[14], AFIP (Armed Forces Institute of Pathology) 2006, MSKCC Nomogram (Memorial Sloan Kettering Cancer Center) and TNM classification 2010 (UIJCC) .

Data were computerized in the program SPSS19. Survival analysis and cumulative incidence were obtained by the Kaplan- Meier method. Statistical analysis of significance was performed by Long rank. The significance level was 5 % probability (p=0.05). Other results were distributed in graphics and tables with averages, medians and minimum and maximum values .

RESULTS

After analysis of 77 charts with histological diagnosis of spindle cell neoplasm, were eliminated eight cases due to loss of follow-up. Thus, 69 cases were included with confirmed diagnosis of GIST, either by immunohistochemical or by phenotypic profile of the analyzed blade. Among the cases 97.1% were positive for CD117 and 87% for CD 34. The two cases C-kit negative, GIST was considered by the pathologist due to its expression (Table 1).

TABLE 1 - Immunohistochemical profile

Immunohistochemical	n (%)
CD117	67 (97,1)
CD34	60 (87)
Vimentin	24 (34,8)
Smooth muscle actin	25 (36,2)
Desmin	11 (15,9)
S-100	11 (15,9)
H-Caldesmon	25 (36,2)
Specific muscle actin (HHF-35)	17 (24,6)
CD68	1 (1,4)
CD10	1 (1,4)

The age ranged from 15 to 88 years, mean 59. About 75 % of cases were over 50 years, 22% between 20 and 50 years and only 3% below 20 years, with slight predominance of females (51%). The white race was the most prevalent with 97% of cases. Most patients (64%) were from other geographic region in relation to the hospital site.

The abdominal pain associated with tumor findings in imaging (ultrasound or abdomen CT) were the most frequent (31.9%). Only 10 patients (14.5%) presented with upper gastrointestinal bleeding. Sixteen cases (23.2%) were an intra-operative incidental finding.

The preferred location was the stomach (n=39, 55.1%), followed by the small intestine (n=18, 26.1%), retroperitoneum (n=8, 11.6%) and rectum (n=2), duodenum (n=1), esophagus (n=1) and colon (n=1), totaling approximately 7%. The presence of malignancy associated was in 28.8 % of cases. The three most frequent tumors were adenocarcinoma of stomach (n=8), prostate (n=4) and colon (n=4).

The gold standard treatment whenever possible was surgery with complete resection (Ro resection). However, it was not possible in approximately 1/3 the cases.

In two cases of stomach involvement were identified positive lymph node. These patients received adjuvant imatinib for being considered with residual disease. One patient with primary site in stomach received neoadjuvant treatment with imatinib scheme to be considered initially unresectable and, after 10 months, underwent R0 resection.

Most were >10 cm (34.8%) with an average size of 8 cm ranging from 0.6 to 28 cm. Regarding the mitotic index, 76.8% had <5/50 fields, 18.8% >5/50 fields of which three cases were not evaluated. Histological type mostly found was spindle cell (91.3%) followed by mixed in 5.8% and 2.9% epithelioid.

Among 57 R0 resection 18.5%(n=13) developed recurrence, and the liver was the most affected organ (85.7%). Underwent salvage surgery four cases: one enucleation of liver metastasis, one left hepatectomy, one nodule resection of the abdominal wall and one partial colectomy with hysterectomy.

Twenty nine patients were submitted to imatinib, 13 cases of recurrence, six of unresectable lesions, seven of R2 resection, two of node-positive and one case was treated with adjuvant imatinib due to high risk of recurrence (this patient had private health insurance). The response rate to imatinib showed 69% partial response and 31% with complete response[8]. The overall 5-year survival of patients receiving imatinib was 43%. Patients considered unresectable had exclusively imatinib therapy presenting global survive in 50%.

The adverse effects of imatinib were identified in nine cases, mostly with nephrotoxicity (17.2%). Among other adversities, two had cardiotoxicity, one leucopenia and one dyspeptic syndrome.

Overall survival in five years was 74% and the patients submitted to imatinib had a worse survival, 57%. However, among this group are patients with metastases at the moment of admission, irressecable patients, residual disease and tumor recurrence (13/29 it means 44.8%) justifying the group to have with worse prognosis.

DISCUSSION

GISTs are rare tumors, represent 1-3% of tumors of the gastrointestinal tract and 80% of gastrointestinal mesenchymal tumors. It mainly affects patients with a mean age of 60 years[20]. The occurrence under 40's is rare ranging from 5-20%. When present under 18, GIST is classified as pediatric, or also called GIST SDH deficient, representing less than 1% of the cases[24]. The average age in this series

was 59 years with two cases (2%) less than 20 years.

The preferred location of GIST is the stomach, followed by the small intestine, colon, rectum and esophagus[18]. They are also called e-GIST (extra-gastrointestinal stromal tumor) when located outside the gastrointestinal tract[9]. Among the e-GIST were identified eight (11.6%) all in retroperitoneum.

The clinical presentation is variable and can be diagnosed as palpable abdominal mass associated with imaging or endoscopic finding, or during the investigation of a digestive hemorrhage. There are other symptoms such as anorexia, weight loss, nausea, dysphagia or intestinal obstruction[6]. In this series the symptom of abdominal pain accompanied by the imaging finding was the most common clinical presentation, followed by palpable mass.

The literature shows positivity for CD117 around 95-98%[25]. Other markers such as CD34, SMA, S -100 protein and Desmin respectively range from 60-70%, 30-40%, 5% and <1%. This sample showed 97,1% positives for CD117 and 87% for CD34.

Surgery with R0 resection is the gold standard treatment for these tumors in 70% of cases of non metastatic disease[8]. Among 69 cases, 56 (81.2%) underwent R0 resection (17.4% requiring multiple resection due to adjacent organ invasion).

The literature recurrence rate in five years ranges from 10-40% in resectable patients[19]. The sample recurrence was 19,7%, whereas when patients stratified as NIH 2008 high risk group was 30,4%, AFIP2006 high risk was 38%, MSKCC Nomogram (considering >50% as high risk) was 41% and TNM 2010 (considering IIIA and IIIB as high risk) was 36%.

The preferred site of recurrence is the liver followed by peritoneum[6]. This study found the same sites, with the liver responsible for 85.7% and the peritoneum by 42.8% of the recurrent cases.

The association with other cancers is previously known in the literature[1]. By definition all GIST are malign neoplasm[25]. The main factors that affect the prognosis is the size and the number of mitoses per microscope field identified by NIH criteria - also called Fletcher[8] criteria -, the primary location site according to AFIP (Armed Forces Institute of Pathology) created in 2006 by Miettinen[19] and finally if there is rupture or not, analyzed by Joensuu in 2008[14]. In 2009, in order to creating a tool that would facilitate risk stratification the Memorial Sloan-Dettering Cancer Center has created a nomogram that automatically calculate tumor size, the number of mitoses in 50 fields of microscopy and the primary site, resulting the risk of recurrence at five years after surgery with complete lesion resection[3]. In 2010 the American Joint Committee on Cancer together with other organizations defined a TNM staging for GIST posted on its 7th edition manual[7]. Thus, it can be used different classifications for stratified the risk of recurrence. This sample was analyzed according to AFIP 2006 modified, NIH 2008, TNM and the nomogram criteria.

Imatinib is allowed in Brasilian National Health System in restricted cases mainly in unresectable cases and metastatic or residual disease after resection. Among 69 patients only one received adjuvant treatment (this patient had private health insurance). Thus, after resection and implementation of risk stratification it was rated high risk, therefore received adjuvant imatinib for three years as established in the literature[13].

Overall survival in five years was 74%, with 18 deaths in 12 years of follow-up; however, includes patients treated with imatinib. Patients treated with surgery alone were 40 with global survive of 86% in five years, and six deaths in this group, three were for general causes (myocardial infarction and stroke) and three by other cancers (stomach and lung). Overall survival in literature ranges 28-84% in five years[12,22]. This disparity occurred because survival is not assessed separately as the risk stratification of each patient groups. The high risk group survival was 65% for NIH2008, 71% for AFIP2006 and for MSKCC Nomogram, and 81% for TNM2010. Whereas the overall survival of patients that did not receive imatinib (n=40) was 86% versus 43% (n=29) for patients that received imatinib therapy (in this group, 13 were recurrence cases).

The mean survival of unresectable or R2 resection in literature[3] ranges from18 (pre-imatinib era) to 60 months. The overall survival of unresectable patients and R2 resected was 33.6 months and 36 months respectively. Both received imatinib. The use of imatinib revolutionized the treatment of GIST and is the gold standard treatment according to the risk stratification[26].

However, there are few cases (around 10%) in which KIT expression does not occur. A portion of these cases (less than 4%)[11,18] mutation occurs in other tyrosine kinase receptor, the receptor-alpha gene derived growth factor platelet (PDGFRA). Not least, there is a small class of GIST negative KIT and PDGFRA negative, known as "wild" type. This class seems to have mutations related to four genes involved in the production of succinate dehydrogenase (SDH)[23] and in a gene called BRAF, frequent in patients with melanoma. This group is associated with more sporadic GIST present in syndromes such as Carney-Stratakis and are more resistant to imatinib[5].

Such biomolecular aspects are important, because as the mutations present in those components, information about the resistance to imatinib can be obtained (Table 2).

TABLE 2 - Molecular GIST classification

KIT Exon 11 Exon 9 Exon 13 & 17	first site common mutation (66,9%)
	second site common mutation (9,8%)
	rare site mutation (2%)
PDGFRα Exon 12 & 14 Exon 18	rare site mutation (1,4%)
	uncommon mutation (6,1%)
wild type (KIT negative e PDGFRα negative)	uncertain molecular etiology
GIST family	gernimative line mutation ok KIT and PDGFRα
Pediatric	rare mutation in KIT and PDGFRα
Carney's Triad	absent mutation in KIT and PDGFRα
Neurofibromatosis type1	absent mutation in KIT and PDGFRα

Thus, mutations in exon 9,11,13 and 17 of KIT and 12 and 14 of PDGFR indicate sensitivity to imatinib. In contrast, mutations in exon 18 (D842V) of PDGFR suggest low response to imatinib.

In 2004, was discovered another protein that helps immunohistochemical assessment of diagnosis process of GIST with KIT negative and negative PDGFR: DOG1 (Discovered on Gist-1) also known as anoctamin1 through the expression of the FLJ10261 gene, present in 98 % of GISTs[16,27] and in a minority of other sarcomas.

CONCLUSION

In order to improve GIST treatment is necessary to add the biomolecular analysis to risk stratification. However, for this to occur, incentive in biomolecular research is required, to increase the possibility of patient survival.

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