JBUON 2016; 21(2): 360-365
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Clinical and pathological characteristics and their effect on survival in elderly patients with gastrointestinal stromal tumors

Nil Molinas Mandel[1], Fatih Selcukbiricik[2], Metin Kanitez[2], Suayip Yalcin[3], Deniz Tural[4], Sibel Erdamar[5], Gulen Dogusoy[6], Gokhan Demir[7]

[1]University of Koc, Department of Medical Oncology, Istanbul; [2]American Hospital, Department of Medical Oncology, Istanbul; [3]Hacettepe University, Faculty of Medicine, Internal Medicine, Department of Medical Oncology, Ankara; [4]Bakirkoy Sadi Konuk Education and Research Hospital, Department of Medical Oncology, Istanbul; [5]Bilim University, Faculty of Medicine, Department of Pathology, Istanbul; [6]Istanbul University, Cerrahpasa Faculty of Medicine, Department of Pathology, Istanbul; [7]Acibadem University, Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey

Summary

Purpose: *Gastrointestinal stromal tumors (GISTs) are common tumors of the gastrointestinal tract. Their most frequent location is the stomach. Although the clinical and pathological characteristics of the disease are well-known, the clinical and pathological characteristics and the response to treatment are not clear in elderly patients. The purpose of this study was to evaluate the characteristics of GISTs in elderly patients with an aim at improving the therapeutic methodology and survival.*

Methods: *In this study, clinicopathological characteristics, evaluation of treatments administered and survival analyses were performed in patients aged 65 years or above, whose data were registered via a web-based patient records system following admission to three centers.*

Results: *A total of 85 patients aged 65 years or above were included in the study. According to the risk classification, 24 (28.2%) were in the low risk group, 20 (23.5%) in the moderate risk group, and 41 (48.3%) in high risk group, while no patient was in the very low risk group. At baseline, 70% of the patients had localized disease and 30% metastatic disease. The tumor was located in the stomach in the majority of the patients (45.6%). The tumor size most commonly seen was 5-10 cm (N=31; 36.4%). Of the 85 patients 23 (27%) were treated with imatinib 400 mg/d. Eight patients (9.4%) with metastatic disease switched from imatinib to sunitinib. At a median follow-up of 76 months (range 1–323), median overall survival (OS) was 72 months, without significant difference between elderly and younger patients.*

Conclusion: *Clinicopathological characteristics and their prognostic impact on the disease course of elderly GIST patients should be elucidated in depth. Since age didn't show prognostic importance, other parameters should be used as prognostic/predictive factors in the tyrosine kinase inhibitors era in order to obtain improved therapeutic results.*

Key words: *gastrointestinal stromal tumor, imatinib, old age, survival, treatment*

Introduction

GISTs are the most common connective tissue tumors of the gastrointestinal tract [1]. GISTs originate from the interstitial cell of Cajal. The majority of GISTs are associated with activating mutations in the KIT gene or platelet-derived growth factor receptor alpha (PDGFRα). Mutation of KIT or PDGFRα plays an important role in the earliest genetic events leading to GISTs formation [2-4].

GISTs affect equally females and males al-

Correspondence to: Fatih Selcukbiricik, MD. University of Koc, Department of Medical Oncology, 40, Davutpasa street, Topkapi, 34200, Istanbul, Turkey. Tel: +90 212 3735000, Fax: +90 212 4143017, E-mail: fsbiricik@yahoo.com
Received: 21/08/2015; Accepted: 07/09/2015

though some reports suggest that GISTs are seen slightly more often in men than in women. Although GISTs can be seen at any age, they most commonly occur betwen 40-80 years (median age 60 years). The most common organ sites are stomach (50–60%), small intestine (20–30%), colon and rectum (10%), esophagus (5%) and duodenum (3–5%) [5,6]. Although the clinical spectrum shows variations, 70% of the patients present symptoms at the time of diagnosis. Asymptomatic patients are diagnosed incidentally during abdominal surgery, endoscopy and radiologic examination [7].

Only limited number of studies on GISTs in the elderly have been reported. However, a previous study has demonstrated that the prognostic factors of GISTs in the elderly are not different than those seen in young patients, and the survival outcomes are also similar [8].

Patients usually present nonspecific symptoms such as nausea, dyspepsia and atypical pain. Symptoms are generally ambiguous in tumors smaller than 2 cm, while larger tumors are usually symptomatic [9].

Surgical resection of the primary tumor is the gold standard treatment for resectable GISTs. Lymph node metastasis of GISTs is unusual, so routine lymphadenectomy is not required [10]. Complete resection, the goal of surgery for GISTs, must be done without capsule rupture and intra-abdominal spread of tumor cells [11].

Imatinib is standard treatment for patients with locally advanced, metastatic or recurrent disease. The recommended dose is 400 mg daily. Imatinib is easily tolerated in the elderly [10]. Mitotic index, tumor size and location are the three risk factors for recurrence in patients treated with imatinib. Age does not influence tumor recurrence [12].

Methods

In this study, a web-based patient records system was used, which was prepared for the records of patients diagnosed with GIST prospectively or retrospectively following admission to three centers. Clinical characteristics of the patients were recorded by the clinician to the network, and pathological characteristics were recorded by the pathologist. The accuracy of the information was checked by the clinician. Age, gender, tumor localization, mitotic index and tumor size were recorded and Fletcher risk classification was performed [13]. In terms of tumor diameters, ≤5 cm, 5-10 cm and > 10 cm were used to stratify risk groups. Mitotic numbers were classified as 0-1, 2-4, 5-10 and >10 in 50 high power fields (HPF). Patients were classified in the following risk groups: very low, low, moderate and high risk.

The general clinical and pathological characteristics of patients were specified as follows: gender, age, ECOG performance status, disease stage, primary tumor localization, tumor size, number of mitoses and histological subtype (spindle cell, epithelioid cell, mixed cell) [14].

Patients in the geriatric age group (≥65 years) were included in the study. The age of 65 years is a cut-off for geriatric age, and the risk of all cancer types occurrence after this age is even 10-fold higher compared to young individuals [15].

Statistics

All data were analyzed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). The survival analyses and curves were generated using the Kaplan-Meier method and compared with the log-rank test. The relapse-free survival (RFS) was defined as the time from curative surgery or diagnosis to recurrence, or to the date of death or loss to follow-up. OS was defined as the time from diagnosis to the date of the patient's death or loss to follow-up. Postrecurrence survival (PRS) was also defined as the time from recurrence to the date of the patient's death or loss to follow-up. Univariate and multivariate analyses were performed using the Cox proportional hazard models to evaluate the importance of clinicopathological features as prognostic factors. Multivariate p values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided and p values less than 0.05 were considered statistically significant.

Results

A total of 85 patients aged ≥65 years were included in the study. The age range was 65-90 years (median 76). Patieht performance status was 0-2. Those with performance status 3-4 were excluded. According to risk classification, 24 patients (28.2%) were in the low risk group, 20 (23.5%) in the moderate risk group, and 41 (48.3%) in the high risk group, while no patient was in the very low risk group. Fifty-five (64.7%) were men and 30 (35.3%) women. Disease localization was in the stomach (45.8%), small intestine (37.6%) and colon (13%). Fifty-nine (69.4%) patients had localized and 26 (30.6%) metastatic disease. Similar results were found in the younger patients.

The patients were classified according to tumor size as follows: 26 (29.9%) <5 cm, 31 (37.3%) >5-10 and 28 (32.8%) >10 cm. According to the mitotic index there were 44 (45.8%) cases with <5 mitoses per 50 HPF and 41 (54.2%) cases with >5 mitoses 50 per HPF.

At a median follow-up period of 76 months (range 1–323), median OS was 72 months (range 12-120). OS according to stage is shown in Figure 1. Five-year survival was 80% in patients with metastatic disease and 88% in those with localized disease (p=0.02). Figure 2 shows RFS with respect to disease stage. Five-year RFS rate for patients with localized disease was considerably better than that of patients with metastatic disease (94 vs 51.6% respectively; p<0.001). Of the 86 patients 23 (27%) were treated with imatinib 400 mg/d, and 8 (9.4%) with metastatic disease switched from imatinib to sunitinib due to disease progression. One patient was treated with palliative radiotherapy. At baseline, the number of patients without metastasis was 61 (71.5%) and the number of patients with metastasis was 24 (28.5%). The patient demographic data are presented in Table 1.

Table 1. General patient and disease characteristics

Characteristics	*N (%)*
Gender	
Men	55 (64.7)
Women	30 (35.3)
Age, years,	
Median (range)	76 (65 – 90)
ECOG PS	
0-1	55 (64.7)
2	19 (22.3)
Unknown	11 (13)
Stage	
Localized	59 (69.4)
Metastatic	26 (30.6)
Primary localization	
Stomach	39 (45.8)
Small intestine	32 (37.6)
Colon	11 (13)
Peritoneum	3 (3.6)
Tumor diameter (cm)	
<5	26 (30.6)
5-10	31 (36.4)
>10	28 (33)
Number of mitoses/50 HPF	
0-1	23 (27)
2-4	16 (18.8)
5-10	20 (23.6)
>10	26 (30.6)
Fletcher classification	
Very low risk group	0 (0)
Low risk group	24 (28.2)
Moderate risk group	20 (23.5)
High risk group	41 (48.3)
Histologic subtype	
Spindle-cell	51 (60)
Mixed-cell	19 (22.3)
Epithelioid	15 (17.7)

HPF: high power field

Discussion

GISTs are the most common mesenchymal tumors of the gastrointestinal tract. The most frequent localization is the stomach both in young and elderly patients. Approximately 10-20 in 1 million individuals are diagnosed with GIST in USA per year and 5000-6000 cases are diagnosed every year. The incidence in Europe is 6.6 in 3-7 million and 14.5 cases per year. Although the disease reaches a peak around the age of 50, it may occur at any age. The highest incidence is seen in the age group of 50-65 years. The male/female incidence is similar; however, some reports suggest a higher incidence in men compared to women [15,16]. GISTs are originated from the Cajal cells which act as the intestinal pacemakers. Gene mutations, mainly KIT (60-80%) and PDGFRA (5-8%) [17], play a key role in malignant transformation [18,19]. Huizinga et al. [20] have shown the important role KIT plays in the development of Cajal cells. Subsequently, Hirota et al. [21] have shown that GISTs commonly express KIT. KIT activation occurs in 80% of all GISTs. This mutation usually affects exon 11 (60%), and more rarely exons 9 (15%), 13 or 17 (5%) [22].

Although GISTs may be seen at any age, they are very rare in young individuals and children. While GISTs are usually seen in the age group of 40-80 years, they are most commonly detected in the 6th decade of life [23]. Only a limited number of studies exist on GISTs in the elderly. The studies on this subject have not shown statistically significant differences in RFS, OS and PFS of elderly patients vs young individuals [6,8,24]. Median OS was 72 months in the present study. Following the launch of the tyrosine kinase inhibitor imatinib [8,25,26], this agent has been shown to provide benefits for the elderly as well as for the young patients. Similar to the case in young individuals, the alternative treatment is sunitinib in the presence of imatinib resistance in the elderly [8,27]. However, extensive studies are required to specify the prognostic factors for sunitinib treatment in the elderly GIST patients.

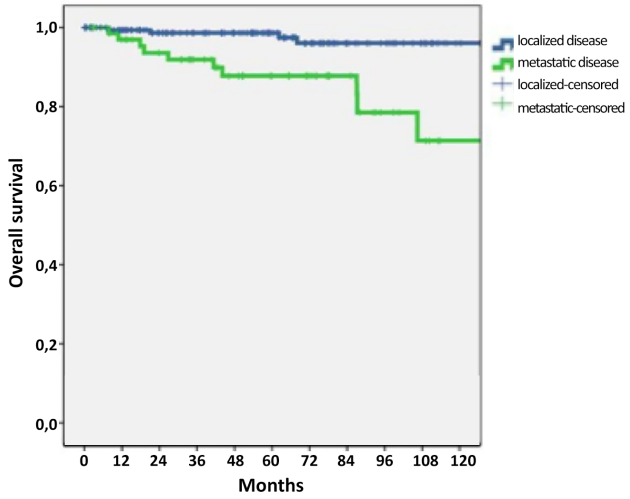

Figure 1. Overall survival according to stage (p=0.02).

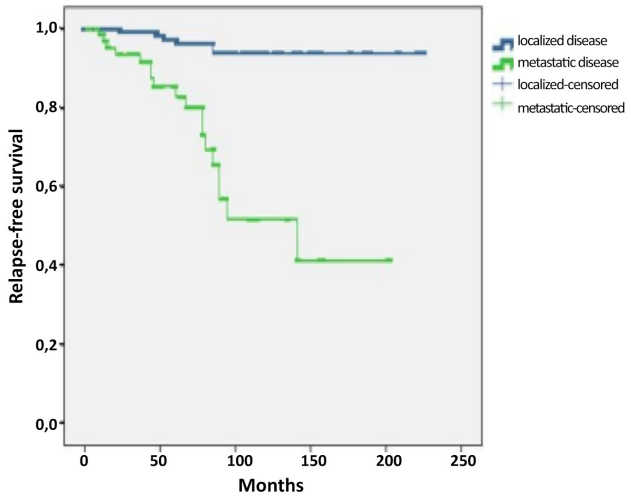

Figure 2. Relapse-free survival according to stage (p<0.001).

Although, to our knowledge, this study has the highest number of elderly GIST patients in the literature, its limitations originate from its retrospective nature. Not including data from young patients and comorbidities of elderly patients prevents the comparison of survivsl between elderly and young patients [28,29].

GISTs are often localized in the stomach, followed by the small intestine; however, they may originate from any region of the gastrointestinal system [29]. In concordance with the literature, the most common localization was the stomach in this study. Relapses in GISTs are associated with the mitotic rate, tumor size and tumor localization. Furthermore, surgical margins and tumor rupture are also important. Several classifications have been developed for disease-related risk classification and relapse prediction. Standard treatment is complete surgical resection in localized disease. Surgical treatment should be segmental resection of the tumor. Careful surgical exploration is important for small peritoneal nodules. Relapse occurs in 40% of completely resected GISTs within 5 years. Mutation type, mitotic rate, tumor size and tumor localization are important risk factors for recurrence [12].

Postoperative adjuvant imatinib may be considered when the patients are metastatic or in high risk group. Adjuvant therapy should be considered particularly during surgery or in case of spontaneous tumor rupture with other risk factors. However, there is no consensus on medical treatment in such occasions [27]. Imatinib is an effective oral therapy with a low toxicity profile, particularly in cases with high recurrence risk following primary resection and in the treatment of small-scale microscopic disease [23,28]. Imatinib treatment is standard therapy in the elderly as well. Unfavorable opinions have not been reported regarding the use of imatinib in the elderly. Adjuvant imatinib 400 mg/d is safe and well-tolerated following complete resection of primary GIST and provides significant improvement in RFS of patients with any tumor size. It is beneficial, particularly in patients having 50% risk of recurrence in 2 years [30].

In GIST patients with high risk of recurrence, adjuvant treatment with imatinib 400 mg/d for 1 year following resection has been well-tolerated. In locally advanced, inoperable and metastatic disease imatinib is the standard treatment [31-33] and should be continued at the same dose (400 mg/d) until disease progression.

In the French Sarcoma Group study (BFR14 study) on discontinuation of imatinib following 3 years of therapy in advanced GIST, rapid progression was observed after discontinuation following medication for 1, 3 and 5 years [34]. There were no cases of drug discontinuation in our patient cohort. In this regard, the time from drug discontinuation to relapse in the elderly was not assessed.

In case of tumor progression, the standard approach is to increase imatinib dose to 800 mg/d. In case of progression during treatment or intolerance to drug, the standard treatment is sunitinib [35]. In the present study the number of patients in whom the imatinib dose was increased to 800 mg/d was 8 and the drug was well-tolerated. In addition, sunitinib was initiated in 8 patients due to disease progression and its tolerance was considerably good.

In conclusion, clinical, pathological and molecular characteristics and their impact on the disease course of elderly GIST patients should be elucidated in depth, in order to develop newer treatment approaches. Since age has not prognostic importance, other parameters should be evaluated as prognostic or predictive factors in the tyrosine kinase inhibitors era to obtain more favorable results in elderly patients

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