DOI: 10.4149/BLL_2015_042

Bratisl Lek Listy 2015; 116 (4)

218 – 221

CLINICAL STUDY

Long term experience of patients with unresectable or metastatic KIT positive gastrointestinal stromal tumours

Kocakova I[1,2], Kocak I[1,2], Spelda S[1], Krejci E[1], Bencsikova B[1], Jureckova A[1], Vyzula R[1], Bortlicek Z[3], Strenkova J[3], Brabec P[3]

Masaryk Memorial Cancer Institute, Brno, Czech Republic. **sspelda@centrum.cz**

Abstract: A retrospective analysis of consecutive patients (183 in total, of which 105 were males and 78 females) with gastrointestinal stromal tumour (GIST) was performed. The mean age was 61 years, median age 64 years. The most frequent localization of the tumour was stomach in 74 patients (40.4 %) and the small intestine in 46 patients (25.1 %). Two or more different synchronous or metachronous cancers occurred in 34 (18.6 %) patients with histologically confirmed GIST. Ninety-six patients were treated with imatinib mesylate in palliative setting during the course of their disease. The therapy was finished in 60 patients and 36 patients have been treated so far. The median progression-free survival reached 32.9 months in the group of 96 patients treated with imatinib. The median overall survival in the group of 96 patients treated for metastatic disease reached 77 months. Two-year and 5-year survival was 85.2 % and 63.1 %, respectively. The second-line therapy with sunitinib malate was administered in 37 patients, of which 31 finished and 6 continued in the therapy. The median progression free survival and median survival since the sunitinib therapy initiation reached 8.4 and 22.1 months, respectively *(Tab. 2, Fig. 2, Ref. 16)*. Text in PDF *www.elis.sk.*

Key words: gastrointestinal stromal tumour, imatinib mesylate, sunitinib malate.

Introduction

Gastrointestinal stromal tumours are thought to arise from mesenchymal stem cells, which also give rise to the interstitial cells of Cajal within the GI tract. Most clinical studies estimate that at least 10–30 % of GISTs are malignant, although their actual clinical potential for locoregional infiltration, recurrence, and distant metastatic spread is not clearly related to histopathologic features (e.g., grade), as it has been demonstrated in other subtypes of sarcomas of non-osseous tissues. GISTs account for approximately 1 % to 3 % of all malignant GI tumours (1). The tumours can arise anywhere in the gastrointestinal tract, the stomach and the small intestine being the most frequent primary sites. The stomach represents 60 % and small intestine 30 % out of all the tumours (2). GISTs characteristically exhibit expression of the CD117 antigen (KIT) examined by immunohistochemical assays, and the levels of expression can vary in different subtypes. CD34 expression is not absolutely specific for GIST; no more than approximately 60 % to 70 % of GIST lesions are CD34-positive (3). CD117-negative GIST represents less than 5 %; these tumours are most likely to be driven by an alternative kinase such as platelet derived growth factor-alpha (PDGFRA) (4). There are no definitive diagnostic criteria of CD117-negative GIST unless the tumour genotype analysis indicates a KIT or PDGFRA mutation. The clinical course may vary depending on the anatomic location, size and aggressiveness of the tumour. Most of the symptomatic patients have tumours larger than 5 cm in maximal dimension. The most reliable prognostic factors for GIST are size of the primary tumour and the mitotic index. Additionally, recurrence and survival rates can be affected by the location of the primary GIST lesion (e.g., primary GIST located in small intestine or rectum demonstrate worse prognosis than gastric GIST). PDGFRA mutations, which almost always mean the primary localization in the stomach, appear to be a favourable factor for low risk of recurrence (5). The consensus on GIST treatment has been adopted and the surgical complete resection of primary GIST is the first choice when possible. Imatinib mesylate, a tyrosine kinase inhibitor of KIT, PDGFR and BCR-ABL, is the first effective drug treatment for patients with KIT positive unresectable and/or metastatic malignant GIST. Imatinib has dramatically improved the overall survival (OS) as well as the quality of life of metastatic GIST patients (6).

Nevertheless, resistance to imatinib develops during the course of treatment in most of the patients. Sunitinib malate has been proved to be efficient in this setting. This drug may further prolong GIST patients' survival.

In this paper we present a retrospective analysis of consecutive GIST patients that visited the Masaryk Memorial Cancer Institute in Brno for the treatment or follow-up since 2003.

[1]Masaryk Memorial Cancer Institute, Brno, Czech Republic, [2]Masaryk University, Faculty of Medicine, Brno, Czech Republic, and [3]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic

Address for correspondence: S. Spelda, MD, Masaryk Memorial Cancer Institute, Zluty kopec 7, CZ-656 53 Brno, Czech Republic.
Phone: +420.5.43136803, Fax: +420.5.43132455

Acknowledgement: The work was supported by MH CZ (Czech Ministry of Health) – DRO (MMCI, 00209805).

Materials and methods

All the consecutive patients with the diagnosis of GIST were entered into the database for further evaluation. The database system has been developed and operated in cooperation with other specialized cancer centres in the Czech and Slovak Republic and Institute of Biostatistics and Analysis of Masaryk University in Brno, Czech Republic. The database system enables the collection and processing of data on GIST patients' diagnosis and treatment (7). The data was analyzed as of August 1, 2013.

Standard descriptive statistics was used to characterize the sample data set. Both overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method. OS was defined as the time from treatment initiation to death due to any cause. PFS was defined as the time from treatment initiation to the disease progression or death due to any cause. All point estimates were accompanied by 95% confidence interval (95% CI).

Results

The overall number of Masaryk Memorial Cancer Institute patients included in the database reached 183 patients, of which 105 were males and 78 females (Tab. 1). The mean age was 61 years, median age 64 years (minimum and maximum age 28 and 79 years, respectively). The most frequent localization of the tumour was stomach in 74 patients (43.3 %) and the small intestine in 46 patients (26.9 %). The primary tumour size reached over 10 cm in 62 patients (36.3 %). Tumours measuring from 6 cm to 10 cm were diagnosed in 48 patients (28.1 %), tumours of a diameter from 2 cm to 5 cm were found in 52 (30.4 %) patients. Nine (5.3 %) patients were diagnosed with the primary tumour smaller than 2 cm. The size of the primary tumour was not specified in 12 patients. The extent of the disease at the time of diagnosis was as follows: limited tumour with the possibility of resection in 127 (70.2 %) patients, locally advanced tumour without the chance for radical resection in 20 (11.0 %) patients, metastatic disease was found in 34 (18.8 %) patients and the primary staging was not specified in 2 patients. Two or more different synchronous or metachronous cancers were present in 34 (18.6 %) patients with histologically confirmed GIST. The increased incidence of multiplied cancers with the presence of GIST has been described in literature (8). There were 60 males and 36 females with the median age 63 years and mean age 60 years who were treated with imatinib mesylate in palliative setting during the course of their disease. The therapy was initiated with daily dose 400 mg. The imatinib therapy was finished in 60 patients and 36 patients have been treated so far.

Tab. 1. Patients characteristics.

	All patients (n=183)
Men, n (%)	105 (57.4)
Age at diagnosis, median (min-max)	64 yrs (28–79)
Localization of primary tumour, n (%)	
stomach	74 (43.3)
small intestine	46 (26.9)
other	51 (29.8)
Size of primary tumour	
< 2 cm	9 (5.3)
2–5 cm	52 (30.4)
6–10 cm	48 (28.1)
10+ cm	62 (36.3)
Extent of disease at diagnosis	
localized resectable	127 (70.2)
locally advance unresectable	20 (11.0)
metastatic	34 (18.8)
Tumour duplicity, n (%)	34 (18.6)

The response to imatinib was as follows: complete response (CR) in 21 (21.9 %), partial response (PR) in 42 (43.8 %), stable disease (SD) in 18 (18.8 %), progressive disease (PD) in 11 (11.5 %) patients. The response to therapy with imatinib was not evaluated in 4 (4.2 %) patients.

In the group of 96 patients treated with imatinib for metastatic disease, the median progression free survival and overall survival reached 32.9 months (95% CI 22.9–43.0) and 77.0 months (95% CI 57.9–96.1) months, respectively. Two-year overall survival was 85.2 % and 63. 1% of patients have lived for 5 years.

The second-line therapy with sunitinib malate was administered in 37 patients with disease progression on imatinib therapy. Sunitinib was administered for 4 weeks followed by 2-week pause and then repeated until progression or toxicity. Thirty-six patients tolerated maximal sunitinib daily dose 50 mg. The regimen with daily dose 37.5 mg was administered in one patient.

The sunitinib-treated patients were 28 males and 9 females with the median and mean age 62 and 63 years, respectively. The therapy was terminated in 31 patients and has continued in 6 ones.

In 37 patients treated with sunitinib, the median progression free survival and overall survival reached 8.4 months (95% CI 4.2–12.5) and 22.1 (95% CI 15.8–28.4) months, respectively. Two-year overall survival was estimated as 43.1 %. The survival analysis of is depicted in Table 2 and Figures 1 and 2.

Some of the patients who had failed the second-line of the sunitinib therapy were recruited for the therapy with regorafenib in compliance with the definition of an expanded access program. For the time being, it has not been possible to analyze the results yet.

Tab. 2. Progression-free and overall survival from imatinib or sunitinib treatment initiation.

Imatinib (n=96)	Median (95% CI)	2 year survival (95% CI)	5 year survival (95% CI)
Progression free survival	32.9 months (22.9–43.0)	63.4% (53.4–73.4)	33.0% (22.5–43.5)
Overall survival	77.0 months (57.9–96.1)	85.2% (77.8–92.7)	63.1% (51.9–74.3)
Sunitinib (n=37)	Median (95% CI)	1 year survival (95% CI)	2 year survival (95% CI)
Progression free survival	8.4 months (4.2–12.5)	45.1% (27.8–62.4)	27.3% (11.2–43.4)
Overall survival	22.1 months (15.8–28.4)	79.1% (64.0–94.2)	43.1% (23.9–62.4)

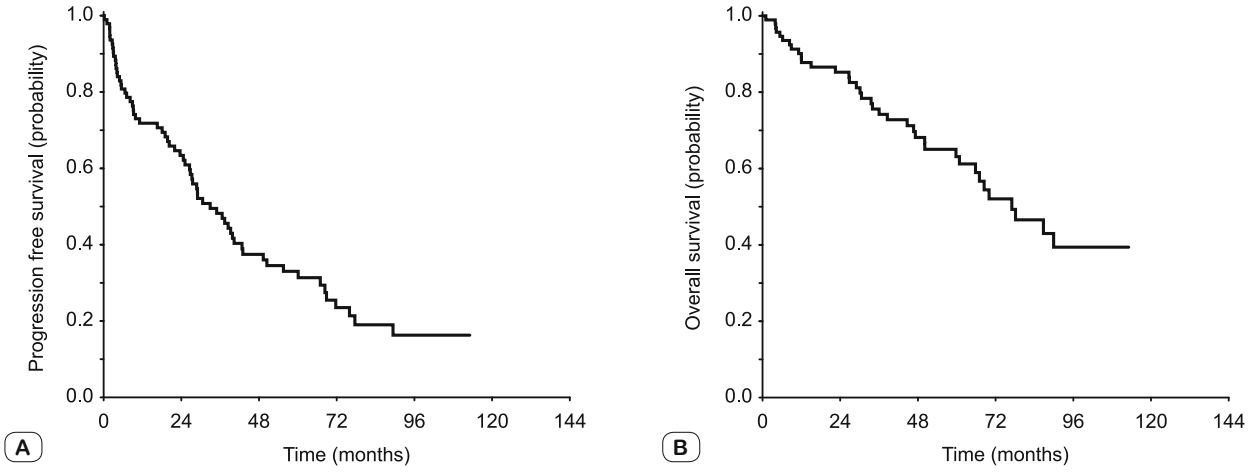

Fig. 1. Progression free survival (A) and overall survival (B) since imatinib treatment initiation.

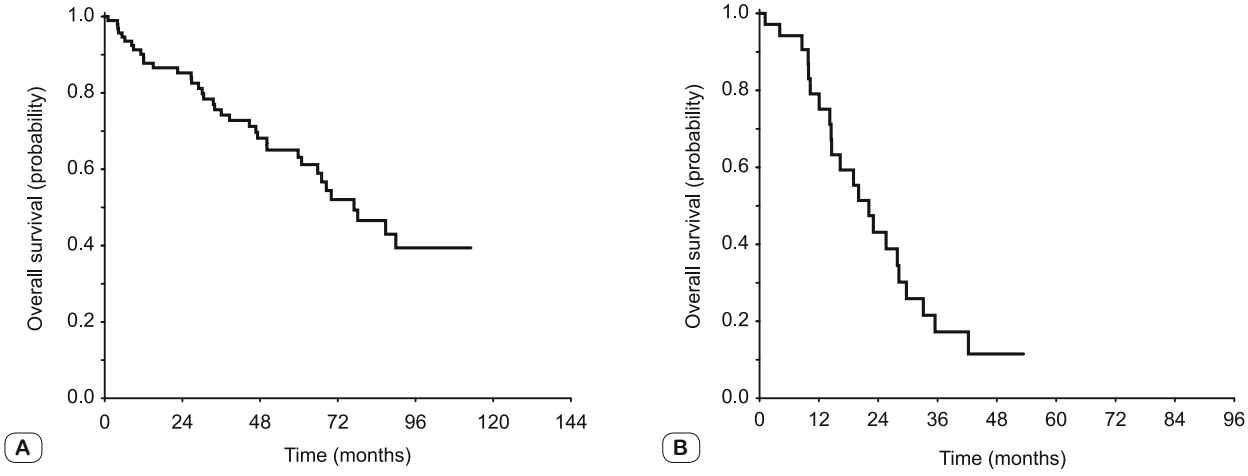

Fig. 2. Progression free survival (A) and overall survival (B) since sunitinib treatment initiation.

Discussion

Most GIST are caused by gain-of-function mutations of the c-kit or PDGFR genes, which induce tumour cell proliferation. In the past, treatment options for patients with metastatic or unresectable disease were limited because of the generally poor response of GIST to any chemotherapy or radiotherapy. Imatinib inhibits BCR-ABL, KIT and PDGFR proteins in vitro and has been found to be clinically effective against GIST (9). The phase II B2222 study demonstrated that imatinib treatment achieved excellent high objective response rates in patients with unresectable or metastatic GIST (6). Many clinical trials have concluded that patients with recurrent or unresectable GIST may reach median survival of 4–5 years (10, 11, 12). The5-year relative survival can be expected from 53.9 % to 74.7 % (13). The 5-year relative survival of 63.1 % presented in our study falls within the mentioned range.

The imatinib therapy duration is another factor associated with progression. According to the B2222 study, progression was observed 2 years after the imatinib treatment initiation and the number of patients with progression was accumulating year by year. Therefore, the size of the primary tumour, the duration of imatinib treatment and the anatomical location of the primary site are related to the development of secondary resistance to imatinib treatment and might be linked to both PFS and OS. As Miettinen and Lasota have reported (2) regarding the risk stratification of metastases or tumour-related deaths in tumour location, the gastric GIST presented a lower risk of recurrence than the other sites, including small intestine, colon and rectum GIST. However, there is an option for second-line therapy for the patients who progress on imatinib, since sunitinib malate was found to be beneficial in this setting. The therapy with sunitinib malate prolonged the progression-free survival (24.1 weeks vs 6.0 weeks; $p < 0.001$) and improved overall survival (HR: 0.49; 95% CI: 0.29 to 0.83; $p = 0.007$) (14). Sunitinib malate therapy induced a partial response in 6.8 % of patients vs 0 % with placebo and durable stable disease ≥ 22 weeks in 17.4 % patients vs 1.9 % patients treated with placebo (15). The reported progression-free survival 8.4 months seemed to confirm the above mentioned data. The acquired resistance to

the tyrosine kinase inhibitors has been an unresolved problem yet, because most of the patients develop the resistance in the course of the treatment. Regorafenib has shown the activity in the patients pretreated with imatinib and sunitinib and has been recently approved by FDA in this setting (16). Regorafenib has not been registered for treatment of resistant GIST in the European Union to date. In our institution we have had an access to regorafenib on the basis of an expanded access program and several individual patients were offered to participate in this program. Nevertheless, the results have not been available yet.

Conclusions

Imatinib has a high efficacy in patients with unresectable and/or metastatic KIT positive GIST during long-term follow-up. The unresolved problem has been the development of resistance to imatinib and sunitinib during the therapy. The risk of developing resistance tends to depend on the tumour size, the localization of primary GIST and the mutation variants. The new drug regorafenib may further improve the therapeutic results of patients with GIST.

References

1. Cassier PA, Ducimetière F, Lurkin A et al. A prospective epidemiological study of new incident GISTs during two consecutive years in Rhone Alpes region: incidence and molecular distribution of GIST in a European region. Br J Cancer 2010; 103 (2): 165–170.

2. Miettinen M, Lasota J. Gastrointestinal stromal tumours: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23 (2): 70–83.

3. Fletcher CD, Berman JJ, Corless C et al. Diagnosis of gastrointestinal stromal tumours: a consensus approach. Hum Pathol 2002; 33: 459.

4. Heinrich MC, Corless CL, Duensing A et al. PDGFRA activating mutations in gastrointestinal stromal tumours. Science 2003; 299: 708.

5. Corless CL, Ballman V, Antonescu C et al. Relation of tumour pathologic and molecular features to outcome after surgical resection of localized primary gastrointestinal stromal tumour (GIST): Results of the intergroup phase III trial ACOSOG Z9001. ASCO Meeting Abstracts 2010; 28 (Suppl 15): 10006.

6. Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumours. N Engl J Med 2002; 347: 472–480.

7. Brabec P, Sufliarsky J, Linke Z et al. A whole population study of gastrointestinal stromal tumours in the Czech Republic and Slovakia. Neoplasma; 2009, 56: 459–464.

8. Agaimy A, Wunsch PH, Sobin LH, Lasota J, Miettinen M. Occurrence of other malignancies in patients with gastrointestinal stromal tumours. Semin Diagn Pathol 2006; 23 (2): 120–129.

9. Joensuu H, Roberts PJ, Sarlomo-Rikala M et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumour. N Engl J Med 2001; 344: 1052–1056.

10. Verweij J, Casali PG, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumours with highdose imatinib: randomised trial. Lancet 2004; 364: 1127–1134.

11. Blanke CD, Demetri GD, von Mehren M et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumours expressing KIT. J Clin Oncol 2008; 26: 620–625.

12. Tryggvason G, Kristmundsson P, Orvar K Jónasson JG, Magnússon MK, Gíslason HG. Clinical study on gastrointestinal stromal tumours (GIST) in Iceland, 1990–2003. Dig Dis Sci 2007; 52: 2249–2253.

13. Rubió J, Marcos-Gragera R, Ortiz MR et al. Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. Eur J Cancer 2007; 43: 144–148.

14. Demetri GD, van Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomized controlled trial. Lancet 2006; 368: 1329–1338.

15. Casali PG, Garrett CR, Blackstein ME et al. Updated results from a phase III trial of sunitinib in gist patients (pts) for whom imatinib (im) therapy has failed due to resistance or intolerance. Proc Am Soc Clin Oncol 2006; 24.

16. Demetri GD, Reichardt P, Kang YK et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381 (9863): 295–302.

Received February 18, 2014.
Accepted March 6, 2014.