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ORIGINAL ARTICLE

Identification of prognostic factors in patients with metastatic gastrointestinal stromal tumors

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Summary

Purpose: *Gastrointestinal stromal tumors (GISTs) have a complex biology which is reflected by a marked clinical heterogeneity. Thus, there has been great interest in identifying prognostic factors influencing tumor recurrence and survival. The aim of this study was to identify potential clinical and immunohistochemical prognostic factors that may affect survival and treatment outcomes in patients with metastatic GISTs.*

Methods: *Between 2000 and September 2011, a total of 41 patients with metastatic GISTs (29 males and 12 females; mean age: 57.4±11.8 years; range 29-74) were referred to the Department of Oncology, Uludag University Medical School. Survival analysis for a number of potential prognostic factors was made with the main outcome results of progression-free survival (PFS) and overall survival (OS).*

Results: *The most common sites of isolated metastases comprised the liver (n=18), followed by lymph nodes (n=5), the omentum (n=1), and the mesothelium (n=1). The remaining patients had metastases at multiple sites. Cox regression analysis identified ileal location as the only significant predictor of poor PFS both after first-line (p=0.023) and second-line therapy (p=0.016). Tumor location in the ileum (p=0.025) and S100 immunoreactivity (p=0.041) were both independent predictors of OS.*

Conclusion: *Tumor site and S100 positivity were the main significant independent predictors of clinical outcomes in patients with metastatic GISTs treated by standard of care.*

Key words: gastrointestinal stromal tumors, prognosis, S100 marker, tumor location

Introduction

GISTS are the most common mesenchymal tumors of the gastrointestinal tract, comprising 1-2% of all of gastrointestinal malignancies [1-3]. The most common GIST sites are the stomach (60%), small intestine (35%), and colorectum (<5%). Approximately 20-25% of gastric and 40-50% of small intestinal GISTs are malignant [4,5].

The cellular origin, differentiation, nomenclature, and prognosis of GISTs has been only partially elucidated [6-8]. Since GISTs behaved similar to the interstitial cells of Cajal expressing the oncogene marker cKit protein (CD117), the Cajal cells were suggested as the origin of GISTs [9,10]. The consensus system proposed by the National Institute of Health in 2001 is the one of the most commonly used grading systems, but it significantly overestimated the biologic potential of gastric GISTs [11,12]. The main prognostic parameters are the tumor size and the tumor site [11,13,14]. Surgical management and the use of imatinib mesylate (IM) are the gold standards of therapeutic care for patients with GISTs [15-17].

IM, a tyrosine kinase inhibitor, is a drug for the treatment of advanced GISTs; it blocks the activity of cKit, ultimately leading to differentiation and apoptosis of GIST cells [18,19]. Unfortunately, a large proportion of patients with advanced GISTs treated with IM developed resistance, especially in the presence of liver and peritoneal metastases [20]. The mechanisms of IM resistance are currently under intensive investigation [20]. In patients with advanced IM-resistant GISTs, sunitinib (a multi-targeted receptor tyrosine kinase inhibitor) has been shown to prolong time to tumor progression and

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survival [21]. Therefore, sunitinib has been approved for the treatment of GIST after disease progression on IM and is recommended for this purpose in current clinical practice guidelines [21].

The complex biology of GISTs is reflected by a marked clinical heterogeneity [4]. Thus, there has been great interest in identifying prognostic factors influencing tumor recurrence and survival [6,11]. The aim of this study was to identify potential prognostic factors that may affect survival and treatment outcomes in patients with metastatic GISTs.

Methods

This study was performed according to the Declaration of Helsinki, and approval was granted by the Institutional Review Board of the Uludag University School of Medicine. All participants gave written informed consent.

Between 2000 and September 2011, a total of 41 patients with metastatic GISTs (29 males and 12 females; mean age: 57.4±11.8 years, range 29-74) were referred to the Department of Oncology, Uludag University Medical School. GISTs were defined as spindle cell or epithelioid neoplasms primary in the gastrointestinal tract, omentum, or mesentery, among the group of combined smooth muscle and stromal tumors. Excluded were other specific entities, such as histologically typical leiomyomas and leiomyosarcomas, inflammatory myofibroblastic tumors, inflammatory fibroid polyps, desmoids, and schwannomas.

Patient data included sex, age, tumor size, site of the primary tumor, type of surgical resection, histological grade, site(s) of metastasis, the dose of IM used in first-line therapy, PFS after first-line therapy, side effects, type of second-line therapy, PFS after second-line therapy, type of third-line therapy, and OS. Unresectability of the primary tumor was defined by size, need for resection of surrounding organs, or major vessel involvement [22].

Immunostaining was performed using the avidin-biotin-peroxidase complex detection technique using LSAB kit (DAKO, Carpinteria, CA) or Vectastain Elite kit (Vector Labs, Burlingame, CA), as previously described [23]. The staining reactions were interpreted only in the presence of internal controls. The immunoreactivity was tested for the following markers: CD117 (tissue mast cells or Cajal cells), CD34 (endothelial cells or perimuscular fibroblasts), SMA (vascular pericytes and smooth muscle), S100 protein (nerves or dendritic antigen-presenting cells), and desmin.

Statistical considerations

Descriptive statistics included counts, means, medians, ranges, and standard deviations, as appropriate. OS was calculated from the date of surgery to the date of last follow-up or date of death. PFS was calculated from the first day of first- or second-line therapy. The data were censored at the date of the last follow-up, date of the appearance of a new lesion or date of reactivation or appearance of any lesion. Univariate and multivariate Cox regression models were used to identify independent predictors of outcome. A forward selection procedure was used to build the multivariate models. All statistical analyses were performed using the SPSS 11.0 statistical package (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

Results

The general characteristics of the study participants are depicted in Table 1. Of a total of 41 patients with metastatic GISTs 3 had unresectable primary tumors, whereas the tumor was partially resectable in another 2 patients. All the remaining patients underwent complete tumor resection. The initial tumor site was the ileum (n=16, 39%), stomach (n=13, 31.7%), duodenum (n=4, 9.8%), rectum (n=3, 7.3%), pancreas (n=2, 4.9%), and retroperitoneum (n=3, 7.3%). The most common forms of clinical presentation were abdominal pain (n=11, 26.8%), abdominal distension (n=10, 24.3%), gastric bleeding (n=9, 21.9%), bowel obstruction (n=8, 19.5%), jaundice (n=2, 2.9%), and diarrhea (n=1, 2.6%). The primary tumor size was < 5 cm in 2 patients, 5-10 cm in 19 patients, and > 10 cm in the remaining 19 patients. Six (14.6%) patients had low-grade tumors, 5 (12.2%) had intermediate-grade GISTs, while the remaining 30 (73.2%) patients had high-grade neoplasms. The most common sites of isolated metastases were seen in the liver (n=18, 43.9%), followed by lymph nodes (n=5, 12.2%), the omentum (n=1, 2.6%), and the mesothelium (n=1, 2.6%). The remaining patients had metastases at multiple sites.

CD117 was positive in all but one GISTs. S100 immunostaining was positive in 5 (12.2%) GISTs. CD34, SMA, and desmin were positive in 22 (53.6%), 16 (39%), and 2 (4.9%) tumors, respectively.

Forty patients received IM 400 mg daily as first-line therapy, whereas one patient received IM 800 mg daily. Of the 41 patients, 3 (7.3%) achieved complete response to first-line therapy, 23 (56.1%) partial response, 13 (31.7%) remained stable, and the remaining 2 (4.9%) showed disease progression. The mean PFS after the first-line therapy was 24±12 months (median=26 months; interquartile range = 12-32 months). The most common side effects were gastrointestinal intolerance (n = 22, 53.6%), and leg edema (n = 2, 4.9%).

Eighteen patients (43.9%) received second-line

Table 1. General patient and disease characteristics (n = 41)

Characteristics	
Gender (male/female)	29/12
Age (years)	57.4±11.8
Unresectable primary GIST (yes/no)	3/38
Metastasis at multiple sites (yes/no)	16/25
CD117 positivity (yes/no)	40/1
S100 positivity (yes/no)	5/36
CD34 positivity (yes/no)	22/19
SMA positivity (yes/no)	16/25
Desmin positivity (yes/no)	2/39

therapy; sunitinib was used in 2 patients and IM 800 mg daily in the remaining 16. Of them, one (5.5%) showed a partial response, 15 (83.3%) remained stable, and 2 (11.2%) had disease progression. The mean PFS after the first-line therapy was 13 ± 8 months (median=11 months; interquartile range=8-17 months).

Eight patients (19.5%) received third-line therapy with sunitinib. At the date of last follow-up, all subjects who received third-line treatment were alive. The mean OS in this subgroup from the date of surgery was 51±18 months (median = 50 months; interquartile range=40-60 months).

The results of univariate and multivariate Cox regression analysis for PFS and OS are shown in Tables 2 and 3, respectively.

Cox regression multivariate analysis identified ileal location as the only significant predictor of poor PFS both after first-line (p=0.023) and second-line therapy (p=0.016). Tumor location in the ileum (p=0.025) and S100 immunoreactivity (p=0.041) were both independent predictors of OS. Figure 1 shows OS according to S100 immunoreactivity.

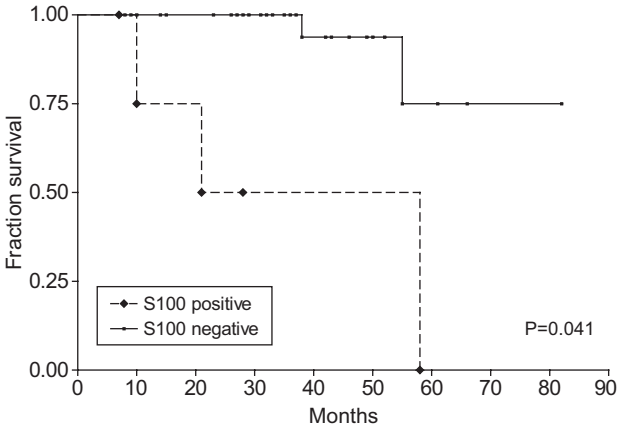

Figure 1. Kaplan-Meier curve of overall survival according to S100 immunoreactivity.

Discussion

In this paper, we described the first data over the prognostic factors in Turkish patients with metastatic GISTs treated with different first-, second-, and third-line therapeutic schemes. We demonstrated that tumor site was the main significant independent predictor of OS and DFS. We also found that immunohistochemical expression of S100 in the primary tumor is independently associated with OS. If independently validated, these data might potentially help identify GISTs with the highest risk of therapeutic failure.

GISTs comprise a series of rare tumors arising from the wall of the gastrointestinal tract, from the esophagus to the rectum [1-7]. These tumors typically present in adults over 40 years and only exceptionally in children. In general, the characteristics of our Turkish patients with GISTs were in line with the published data, which show a mean age of patients of approximately 60 years and a predominant localization of the tumors in

Table 2. Univariate Cox proportional hazard regression analysis for predictors of overall survival and progression-free survival

Characteristics	*Overall survival*	*Progression-free survival*
Gender	HR = 1.2 (95% CI = 0.8-1.5, P = ns)	HR = 1.1 (95% CI = 0.7-1.6, P = ns)
Age	HR = 1.4 (95% CI = 0.9-2.2, P = ns)	HR = 1.6 (95% CI = 0.7-1.9, P = ns)
Unresectable primary GIST	HR = 1.8 (95% CI = 0.9-3.4, P = ns)	HR = 1.4 (95% CI = 0.8-3.6, P = ns)
Metastasis at multiple sites	HR = 2.5 (95% CI = 0.5-3.9, P = ns)	HR = 2.8 (95% CI = 0.8-3.6, P = ns)
CD117 positivity	HR = 1.9 (95% CI = 0.5-5.6, P = ns)	HR = 1.5 (95% CI = 0.6-5.1, P = ns)
S100 positivity	HR = 1.5 (95% CI = 1.1-3.4, P = 0.012)	HR = 1.4 (95% CI = 1.1-3.6, P = 0.042)
CD34 positivity	HR = 1.4 (95% CI = 0.8-1.4, P = ns)	HR = 1.5 (95% CI = 0.9-1.7, P = ns)
SMA positivity	HR = 1.8 (95% CI = 0.6-3.4, P = ns)	HR = 1.9 (95% CI = 0.8-4.5, P = ns)
Desmin positivity	HR = 2.3 (95% CI = 0.5-3.4, P = ns)	HR = 2.9 (95% CI = 0.7-3.2, P = ns)
Ileal location	HR = 1.5 (95% CI = 1.1-1.9, P = 0.007)	HR = 1.6 (95% CI = 1.2-2.4, P = 0.009)
Primary tumor size > 10 cm	HR = 2.4 (95% CI = 0.9-4.1, P = ns)	HR = 2.2 (95% CI = 0.7-3.6, P = ns)

HR: hazard ratio; CI: confidence interval, ns: not significant

Table 3. Multivariate-adjusted Cox proportional hazard regression analysis for predictors of overall survival and progression-free survival

Characteristics	*Overall survival*	*Progression-free survival*
S100 positivity	HR = 1.4 (95% CI = 1.1-3.6, P = 0.041)	HR = 1.4 (95% CI = 1.0-3.2, P = ns)
Ileal location	HR = 1.4 (95% CI = 1.1-2.8, P = 0.025)	HR = 1.5 (95% CI = 1.1-2.8, P = 0.016)

HR: hazard ratio; CI: confidence interval, ns: not significant

the stomach and small bowel [1-7]. The clinical presentation of GISTs is known to be extremely heterogeneous and non specific (vomiting, abdominal pain or distension) [8] and this was further confirmed in our series.

The main finding of our study is the extremely high prognostic significance of the primary tumor site in patients with metastatic GISTs. In particular, we found that metastatic patients with an ileal location of the primary tumor had a worse outcome than subjects with primary tumors at other sites. These data are in accordance with those published by Miettinen and Lasota [3] who showed that all intestinal GISTs have a higher risk for metastases than gastric GISTs. The reasons behind the prognostic significance of the primary tumor site in PFS of GISTs treated by the current standard of care are presently unclear, but could reflect significant differences in tumor biological behavior and aggressiveness. For these reasons, a further aim of this study was to characterize our GISTs in terms of immunohistochemistry.

We found the rate of S100-positivity to have prognostic significance for OS in this series. Interestingly, S100-positivity has been most frequently reported for intestinal GISTs than for gastric tumors. The S100 family has recently emerged as a promising marker in cancer development and progression [24,25]. The S100 name is based on the fact that they are soluble in 100% saturated ammonium sulfate at neutral pH. From a functional standpoint, S100 proteins are involved in a number of different biological processes, including cell differentiation, cell cycle regulation, and cell growth [24,25]. Previous data have shown that the expression of several S100 members is altered in cancer cells compared to normal cells [24]. Importantly, S100 can interact and regulate various proteins involved in cancer and exert different effects on p53 activity [24]. Although the exact mechanisms underlying the prognostic significance of S100 in metastatic GISTs cannot be directly inferred from this study, we believe that our findings provide intriguing preliminary evidence that S100 positivity can serve as a promising prognostic biomarker of metastatic GISTs treated according to the current standards.

The limitations of this study are the homogeneous ethnic background of the study population and that the patients included in the study could be a selected group and may not represent the general population of patients with GISTs. These limitations notwithstanding, our present findings have provided additional and updated information on the characteristics and survival of patients with GISTs, as well as prognostic factors. Some of the findings presented will prove immediately clinically useful for the prediction of prognosis and risk stratification. In most cases, the clinical behavior of a metastatic GIST can be predicted with relative accuracy based on the combination of tumor site and S100-positivity. Hopefully, these data can make some contribution towards improving the outlook for future patients with these rare tumors. Beyond clinical applicability, future work must address mechanistic questions about the functional role of S100 expression in determining the outcome of GISTs.

References

1. Dirnhofer S, Leyvraz S. Current standards and progress in understanding and treatment of GIST. Swiss Med Wkly 2009; 139: 90-102.
2. Nishida T, Hirota S. Biological and clinical review of stromal tumors in the gastrointestinal tract. Histol Histopathol 2000; 15: 1293-1301.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23: 70-83.
4. Candelaria M, de la Garza J, Duenas-Gonzalez A. A clinical and biological overview of gastrointestinal stromal tumors. Med Oncol 2005; 22: 1-10.
5. van der Zwan SM, DeMatteo RP. Gastrointestinal stromal tumor: 5 years later. Cancer 2005; 104: 1781-1788.
6. Paral J, Slaninka I, Kalabova H et al. Gastrointestinal stromal tumors: review on morphology, molecular pathology, diagnostics, prognosis and treatment options. Acta Gastroenterol Belg 2010; 73: 349-359.
7. Liegl-Atzwanger B, Fletcher JA, Fletcher CD. Gastrointestinal stromal tumors. Virchows Arch 2010; 456: 111-127.
8. Nishida T, Takahashi T, Miyazaki Y. Gastrointestinal stromal tumor: a bridge between bench and bedside. Gastric Cancer 2009; 12: 175-188.
9. Duensing S, Duensing A. Targeted therapies of gastrointestinal stromal tumors (GIST)--the next frontiers. Biochem Pharmacol 2010; 80: 575-583.
10. Braconi C, Bracci R, Cellerino R. Molecular targets in gastrointestinal stromal tumors (GIST) therapy. Curr Cancer Drug Targets 2008; 8: 359-366.
11. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis and differential diagnosis. Arch Pathol Lab Med 2006; 130: 1466-1478.
12. Fletcher C, Berman J, Corless C et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002; 33: 459-465.
13. Miettinen M, El-Rifai W, Sobin LH et al. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. Hum Pathol 2002; 33: 478-483.
14. DeMatteo R, Lewis JJ, Leung D et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231: 51-58.
15. Ganjoo KN, Patel S. Current and emerging pharmacological treatments for gastrointestinal stromal tumour. Drugs 2011; 71: 321-330.
16. Reichardt P, Blay JY, Mehren M. Towards global consensus in the treatment of gastrointestinal stromal tumor. Expert Rev Anticancer Ther 2010; 10: 221-232.
17. Valadão M, Linhares E. The role of the surgeon in the management of GIST. Rev Col Bras Cir 2009; 36: 261-265.
18. Lopes LF, Bacchi CE. Imatinib treatment for gastrointesti-

nal stromal tumour (GIST). J Cell Mol Med 2010; 14: 42-50.
19. Cassier PA, Blay JY. Imatinib mesylate for the treatment of gastrointestinal stromal tumor. Expert Rev Anticancer Ther 2010; 10: 623-634.
20. Wang WL, Conley A, Reynoso D et al. Mechanisms of resistance to imatinib and sunitinib in gastrointestinal stromal tumor. Cancer Chemother Pharmacol 2011; 67 (Suppl 1): S15-24.
21. Hopkins TG, Marples M, Stark D. Sunitinib in the management of gastrointestinal stromal tumours (GISTs). Eur J Surg Oncol 2008; 34: 844-850.
22. Bonvalot S, Eldweny H, Péchoux CL et al. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. Ann Surg Oncol 2006; 13: 1596-1603.
23. Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol 2000; 13: 1134-1142.
24. Salama I, Malone PS, Mihaimeed F, Jones JL. A review of the S100 proteins in cancer. Eur J Surg Oncol 2008; 34: 357-364.
25. Emberley ED, Murphy LC, Watson PH. S100 proteins and their influence on pro-survival pathways in cancer. Biochem Cell Biol 2004; 82: 508-515.