Gastric Cancer (2013) 16:596–601
DOI 10.1007/s10120-012-0213-y

SHORT COMMUNICATION

# Molecular characterization of an Italian series of sporadic GISTs

**P. Origone · S. Gargiulo · L. Mastracci · A. Ballestrero · L. Battistuzzi · C. Casella · D. Comandini · R. Cusano · A. P. Dei Tos · R. Fiocca · A. Garuti · P. Ghiorzo · C. Martinuzzi · L. Toffolatti · Liguria GIST Unit · G. Bianchi Scarrà**

Received: 15 June 2012 / Accepted: 4 November 2012 / Published online: 5 January 2013


**Abstract**
*Purpose* Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the gastrointestinal tract. Most (80 %) contain activating mutations in the KIT receptor tyrosine kinase, roughly 10 % in platelet-derived growth factor receptor-alpha (PDGFRA). In a small subset, BRAF mutations are an alternative molecular pathway. GISTs respond well to imatinib, but low response is seen in patients with wild-type KIT or PDGFRA. Resistance has also been reported as a result of mutations in downstream effectors such as BRAF.
*Methods* We provide here a molecular characterization of a series of primary GISTs from Italian patients. Of 121 GIST cases diagnosed between 2000 and 2012, 83 were evaluated by PCR amplification and direct sequencing for mutations in KIT exons 8, 9, 11, 13, and 17, PDGFRA exons 12, 14, and 18, and BRAF exon 15. Eighty-one GISTs also underwent K-RAS testing.
*Results* Sixty-four GISTs were positive: 55 had mutations in KIT and 9 in PDGFRA; 16 patients were mutation negative. Three samples came from NF1 patients and were KIT- and PDGFRA negative. Overall, we identified six novel mutations in KIT (p.K550_M552delinsL, p.Q556_W557delinsG p.Q556_G575del, p.W557_V559delinsQ p.P573_R588dup, p.G592_K593dup) and one novel mutation in PDGFRA (p.D842_N848delinsVDV), thus contributing to widening the spectrum of known mutations in GIST tumors and confirming the most frequently altered regions underlying GIST development.
*Conclusions* Among the 64 KIT- and PDGFRA-positive sporadic patients in our series, no BRAF or KRAS

P. Origone, S. Gargiulo, and L. Mastracci contributed equally to this study.

D. Comandini, F. De Cian, L. Mastracci, G. Bianchi Scarrà and E. Biscaldi are from the Liguria GIST Unit.

P. Origone (✉) · S. Gargiulo · A. Ballestrero · R. Cusano · A. Garuti · P. Ghiorzo · C. Martinuzzi · G. Bianchi Scarrà
Department of Internal Medicine, University of Genova, Viale Benedetto XV, 6, Genoa, Italy
e-mail: origone@unige.it

L. Mastracci · R. Fiocca
Department of Surgical Sciences and Integrated Diagnostic, University of Genoa and Anatomic Pathology Service, IRCCS AOU S. Martino-IST, Genoa, Italy

L. Battistuzzi
Department of Health Sciences, University of Genoa, Genoa, Italy

C. Casella
Liguria Cancer Registry, IRCCS AOU S. Martino-IST, Genoa, Italy

D. Comandini
Medical Oncology Unit, IRCCS AOU S. Martino-IST, Genoa, Italy

A. P. Dei Tos · L. Toffolatti
Department of Pathology and Molecular Genetics, Treviso General Hospital, Treviso, Italy

P. Ghiorzo · G. Bianchi Scarrà
Laboratory of Genetics of Rare Hereditary Cancers, IRCCS AOU S. Martino-IST, Genoa, Italy

mutations were identified, suggesting that co-occurrence of these mutations is likely to be rare in the northwestern Italian population and not a frequent cause of primary resistance to imatinib in KIT-positive GIST patients.

**Keywords** GIST · KIT · PDGFRA · BRAF · KRAS

## Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that develop in the gastrointestinal tract and rarely occur in the mesentery or retroperitoneum. GISTs show strong immunohistochemical staining for CD117, and most (80 %) contain activating mutations in the KIT receptor tyrosine kinase [1]. Roughly 10 % harbor mutations in platelet-derived growth factor receptor-alpha (PDGFRA) [2]. In a small subset of tumors, termed wild-type GISTs, KIT and PDGFRA mutations are absent. BRAF mutations are an alternative molecular pathway in some (7–13 %) KIT and PDGFRA wild-type tumors [3, 4].

GISTs are known to respond well to treatment with imatinib [5, 6], a selective tyrosine kinase inhibitor that interferes with KIT and PDGFRA receptor activation. Low response to imatinib has been observed in patients with wild-type KIT or PDGFRA [7]. Resistance has also been reported as a result of the presence of mutations in downstream effectors such as BRAF [8].

Interestingly, a recent study reported for the first time the presence of both KRAS and BRAF mutations in GISTs that also harbored mutations in KIT and PDGFRA [9].

We provide here a molecular characterization of a series of primary GISTs from Italian patients, most of which are from the northwestern Italian region of Liguria, whom we also tested for presence of KRAS and BRAF mutations to verify the frequency of these mutations in Italian GIST patients.

## Materials and methods

Through the Anatomical Pathology Service of the University of Genoa we retrospectively identified all the cases diagnosed with GIST between January 2000 and April 2012 ($n = 121$). All were primary tumors. The presence of additional tumors was ascertained through the local Cancer Registry.

### Immunohistochemical analysis

Of the 121 tumors, 115 were available for analyses. Six could not be evaluated because of the small size of bioptic fragments. All the cases were reviewed by the same pathologist (L.M.), who confirmed the diagnosis using immunohistochemical reactions for CD117 and DOG1 when appropriate.

### Mutational analysis

Tumor DNA was extracted from the microdissected fragments of formalin-fixed, paraffin-embedded GISTs according to the manufacturer's directions (QIAmp DNA FFPE Tissue Kit; Qiagen, Valencia, CA, USA). A total of 83 (72 %) cases with sufficiently preserved DNA were evaluated for KIT exons 8, 9, 11, 13, and 17, PDGFRA exons 12, 14, and 18, and exon 15 BRAF by polymerase chain reaction (PCR) amplification and direct sequencing as previously described [3, 10]. Analysis of a subset of samples for presence of mutations in KIT and PDGFRA was performed in parallel by the Department of Pathology and Molecular Genetics of Treviso Hospital.

Furthermore, 81 GISTs for which DNA was still available were tested for presence of mutations in KRAS [3].

## Results

One hundred and fifteen patients with GISTs were identified. All cases showed immunohistochemical positivity with CD117 and/or DOG1. At review, three samples were seen to come from NF1 patients, who had been also referred to the local Genetics Service.

Thirty-nine (34.8 %) of the 112 sporadic GIST patients had been diagnosed with additional synchronous or metachronous neoplasia. Table 1 details the additional primary malignant and benign neoplasms associated with GISTs.

### Molecular analyses

DNA suitable for molecular analysis was extracted from formalin-fixed, paraffin-embedded tissues in 80 sporadic GISTs and 3 NF1 patients. We excluded patients with inadequate DNA amplification for mutation analysis.

Mutational analysis was performed for KIT exons 8, 9, 11, 13, and 17 and for PDGFRA exons 12, 14, and 18. Sixty-four GISTs (80 %) were positive: 55 (86 %) had mutations in KIT and 9 (14 %) in PDGFRA; 16 (20 %) patients were mutation negative. As expected, GISTs associated with NF1 were negative for KIT and PDGFRA mutations. Clinicopathological features of GISTs with and without mutations, including the presence of additional cancers, are shown in Table 2.

Among the samples bearing mutations in KIT, 48 showed mutations in exon 11 (87.3 %), 4 in exon 9 (7.3 %), and 3 in exon 13 (5.5 %).

**Table 1** Patients with gastrointestinal stromal tumors (GIST) associated with other primary malignant or benign neoplasms

| Patient number | First tumor (age, years) | Second tumor (age, years) | Third tumor (age, years) |
|---|---|---|---|
| 1 | Bladder cancer (69) | GIST (70) | |
| 2 | Colon cancer (70) | GIST (79) | Meningioma (81) |
| 3 | Prostate cancer (67) | GIST (69) | |
| 4 | GIST (65) | Prostate cancer (67) | |
| 5 | GIST (84) | Colon cancer (84) | |
| 6 | GIST (74) | Breast cancer (74) | |
| 7 | GIST (59) | Stomach cancer (59) | |
| 8 | GIST (78) | Colon cancer (85) | |
| 9 | Breast cancer (65) | GIST (66) | |
| 10 | GIST (67) | Breast cancer (75) | |
| 11 | Esophageal cancer (73) | GIST (74) | |
| 12 | GIST (70) | Monocytic leukemia (72) | |
| 13 | GIST (70) | Pancreatic cancer (70) | |
| 14 | GIST (66) | Lung cancer (73) | |
| 15 | GIST (51) | Breast cancer (53) | |
| 16 | Basal cell carcinoma (67) | GIST (80) | Cutaneous spindle cell carcinoma (80) |
| 17 | GIST (75) | Thyroid cancer (77) | |
| 18 | Bladder cancer (85) | GIST (92) | |
| 19 | GIST (68) | Kidney cancer (68) | |
| 20 | Basal cell carcinoma (55) | GIST (61) | |
| 21 | GIST (74) | Basal cell carcinoma (74) | Stomach cancer (74) |
| 22 | Prostate cancer (68) | GIST (75) | Hodgkin lymphoma (80) |
| 23 | Prostate cancer (56) | GIST (71) | |
| 24 | GIST (66) | Splenic hamartoma (66) | |
| 25 | GIST (91) | Colon cancer (91) | |
| 26 | GIST (72) | Hodgkin lymphoma (72) | |
| 27 | Basal cell carcinoma (73) | GIST (79) | |
| 28 | Cancer of the cecum (70) | GIST (82) | |
| 29 | Breast cancer (72) | GIST (75) | Chronic lymphocytic leukemia (75) |
| 30 | Lung cancer (58) | GIST (75) | |
| 31 | Cancer of the rectum (68) | GIST (69) | Kidney cancer + prostate cancer (69) |
| 32 | Basal cell carcinoma (58) | GIST (69) | Non-Hodgkin lymphoma (69) |
| 33 | Basal cell carcinoma + prostate cancer (78) | GIST (85) | |
| 34 | GIST (82) | Colon cancer (82) | |
| 35 | Non-Hodgkin lymphoma (58) | GIST (59) | |
| 36 | Basal cell carcinoma (69) | GIST (72) | Non-Hodgkin lymphoma (72) |
| 37 | Thyroid adenoma (62) | GIST (68) | |
| 38 | Non-Hodgkin lymphoma (53) | GIST (63) | |
| 39 | GIST (86) | Colon cancer (86) | |

We identified twice a single lesion carrying two different mutations: one harbored a duplication involving codons 571–579 in association with the p.W557X mutation; the other showed two point mutations, p.W557G and p.P551L.

Nine mutation-positive tumors carried PDGFRA mutations; all but one involved codon p.D842. The two point mutations identified are the most frequently reported in the literature. The two frameshift mutations are a novel deletion/insertion and a known deletion [11]. Table 3 details the KIT and PDGFRA mutations identified.

All samples were tested for the presence of the V600E BRAF mutation, and 81 samples were analyzed

**Table 2** Clinicopathological characteristics of sporadic GISTs

| Clinicopathological characteristics | Mutated (64) | WT (16) |
|---|---|---|
| Sex | | |
| Male (%) | 40 (62.5) | 6 (37.5) |
| Female (%) | 24 (37.5) | 10 (62.5) |
| Age | | |
| Median | 66 | 68 |
| Range | 40–92 | 31–84 |
| Primary tumor site | | |
| Stomach (%) | 36 (56.25) | 5 (31.25) |
| Ileum (%) | 5 (7.8) | 4 (25) |
| Jejunum (%) | 8 (12.5) | 3 (18.8) |
| Duodenum (%) | 3 (4.9) | 1 (6.3) |
| Colon (%) | 6 (9.5) | 2 (12.5) |
| Peritoneum (%) | 3 (4.9) | – |
| Retroperitoneum (%) | 1 (1.6) | – |
| Esophagus (%) | – | 1 (6.3) |
| NA | 2 (3.1) | – |
| Cell type (%) | | |
| Epitheloid (%) | 10 (15.6) | 1 (6.3) |
| Spyndle cell (%) | 38 (59.4) | 7 (43.8) |
| Mixed (%) | 16 (25) | 7 (43.8) |
| NA (%) | – | 1 (6.3) |
| Mitotic index (%) | | |
| <5/50 HPF (%) | 43 (67.2) | 13 (81.3) |
| >5/50 HPF (%) | 16 (25) | 2 (12.5) |
| NA (%) | 5 (7.8) | 1 (6.3) |
| Tumor size | | |
| <2 cm (%) | 10 (15.6) | 2 (12.5) |
| >2<5 cm (%) | 19 (29.7) | 6 (37.5) |
| >5<10 cm (%) | 20 (31.2) | 5 (31.25) |
| >10 cm (%) | 13 (20.3) | 1 (6.3) |
| NA (%) | 2 (3.1) | 2 (12.5) |
| Risk | | |
| Very low (%) | 11 (17.2) | 2 (12.5) |
| Low (%) | 16 (25) | 6 (37.5) |
| Intermediate (%) | 9 (14) | 2 (12.5) |
| High (%) | 24 (37.5) | 6 (37.5) |
| NA (%) | 4 (7.8) | – |
| Other malignancies | | |
| Synchronous (%) | 6 (9.5) | 1 (6.3) |
| Before GIST (%) | 7 (10.9) | 4 (25) |
| After GIST (%) | 3 (4.9) | 1 (6.3) |
| Before and synchronous (%) | 2 (3.1) | 1 (6.3) |
| Before and after (%) | – | 1 (6.3) |

*WT* wild type, *NA* not available

for presence of the G12A and/or G13D KRAS mutations. All the samples tested were negative for these alterations.

**Table 3** Mutations identified in KIT and platelet-derived growth factor receptor-alpha (PDGFRA)

| Gene | Type of mutation | | Number of patients carrying mutation |
|---|---|---|---|
| KIT | | | |
| Exon 9 | Duplication | p.A502_Y503dup | 4 |
| Exon 11 | Deletion | p.K550_W557del | 1 |
| | | p.Y553_W557del | 1 |
| | | p.Q556_G575del | 1 |
| | | p.W557_K558del | 3 |
| | | p.W557_E561del | 1 |
| | | p.W557_Q575del | 2 |
| | | p.V559_E561del | 1 |
| | | p.V560del | 2 |
| | | p.Y570_L576del | 1 |
| | | p.Y570_Y578del | 1 |
| | | p.D579del | 8 |
| | | p.H580del | 1 |
| | Point mutation | p.P551L | 1 |
| | | W557G | 1 |
| | | p.W557R | 2 |
| | | p.W557X | 1 |
| | | p.V559A | 1 |
| | | p.V559D | 6 |
| | | p.V560D | 1 |
| | Duplication | p.I571_D579dup | 1 |
| | | p.P573_P585dup | 1 |
| | | p.P573_R588dup | 1 |
| | | p.L576_L589dup | 2 |
| | | p.P577_H580dup | 1 |
| | | p.D579_F591dup | 1 |
| | | p.G592_K593dup | 1 |
| | Insertion | p.D579_H580ins QDPTQLPYD | 1 |
| | Deletion/insertion | p.K550_M552delinsL | 1 |
| | | p.Q556_W557delinsG | 1 |
| | | p.V559_Y573delinsQ | 1 |
| | | p.W557_V559delinsC | 1 |
| | | p.W557_V559delinsF | 1 |
| Exon 13 | Point mutation | p.K642E | 3 |
| PDGFRA | | | |
| Exon 18 | Point mutation | p.D842Y | 2 |
| | | p.D842 V | 5 |
| | Deletion | p.I843_D846del | 1 |
| | Deletion/insertion | p.D842_N848delinsVDV | 1 |

## Discussion

In this study we provide a molecular characterization of 83 primary GIST tumors, 80 of which were sporadic and 3 were diagnosed in NF1 patients.

In our case series most of the KIT mutations identified were located at exon 11, between codon 551 and codon

580, where most of the known mutations have been reported so far [12]. This position has been suggested to be associated with malignant tumor behavior [13, 14]. However, we were unable to establish a genotype–phenotype correlation to confirm this hypothesis. The duplications we identified also lie in the regions previously described [13].

We found two GIST tumors that carried two different mutations each. In one, the known mutation p.W557G occurred along with mutation p.P551L, which has been reported in tissue from salivary gland carcinoma [15]. In the other case, the duplication p.I571_D579dup was associated with the nonsense mutation p.W557X, which was reported previously in the germline of a patient with piebaldism and in bone marrow tissue from a patient with myelodysplastic syndrome [16, 17]. Neither patient was reported to have other tumors, but germline mutational analysis could not be performed. Multiple mutations in tissue samples from a primary tumor have already been described in highly malignant lesions and in recurrent GIST tumors with acquired resistance after chemotherapy [18].

Three other cases were found to carry the p.K642E mutation in exon 13 of KIT, which has been rarely described. It has been suggested that this mutation disrupts normal autoinhibitory function of the juxtamembrane domain [19].

Two missense mutations were detected in seven tumors, both in exon 18 of PDGFRA, at codon 842, confirming that this codon is frequently altered [11, 20]. Moreover, a novel deletion/insertion and a deletion were observed.

By identifying seven novel mutations, six in KIT (p.K550_M552delinsL, p.Q556_W557delinsG p.Q556_G575del, p.W557_V559delinsQ p.P573_R588dup, p.G592_K593dup) and one in PDGFRA (p.D842_N848delinsVDV), our study contributes to widening the spectrum of known mutations in GIST tumors and to confirm the most frequently altered regions underlying GIST development. Detailed characterization of mutations in these receptor tyrosine kinases has become of great value because treatment with imatinib has been found to be effective in targeting lesions with KIT and PDGFRA alterations [21].

Several studies have reported that GIST patients also develop other malignancies and have analyzed the clinical and pathological features of these patients compared to those with GIST alone. In our series, about 30 % of the 112 patients with sporadic GISTs had at least one additional malignant tumor, and the most frequent tumor types observed (colon, prostate, and breast cancer) confirm previous findings by others [22]. The high frequency of other malignancies among our GIST patients (34.8 %) is unlikely related to imatinib therapy since the majority of the additional tumors were observed before the diagnosis of GIST. Underlying genetic instability or mismatch repair may lead to KIT mutation, resulting in GIST, and other oncogenes may explain the presence of other cancers. Furthermore, the lack of information on the family cancer history of the patients and the fact that germline DNA from these patients could not be analyzed does not allow us to rule out the presence of constitutive alterations and thus of hereditary cancer syndromes.

Most of the reports describing co-occurring GIST and other tumors do not include molecular analyses of KIT and PDGFRA to establish potential differences. We performed these analyses and found that the distribution of mutations did not differ according to the patients' cancer history.

Some investigators have been recently focusing on the role of BRAF protein in the development of GIST. BRAF is located immediately downstream of RAS in the MAP-kinase cascade, and most BRAF mutations in GIST are at a hotspot at nucleotide 1799, in exon 15, where a valine is usually substituted for a glutamic acid at codon 600 (V600E). BRAF mutations are thought to be mutually exclusive with KIT or PDGFRA mutations and are more frequently reported in lesions occurring in the small intestine [3, 4]. Recently, a Swiss–Italian study [9] identified, for the first time, a BRAF mutation in a patient who also harbored a KIT mutation from a series of 47 Italian GIST patients with mutations in KIT or PDGFRA. The authors also identified a KRAS mutation in 2 KIT- and 1 PDGFRA-positive patients from a series of 38 Swiss patients with mutations in KIT or PDGFRA. These findings prompted the authors to investigate co-occurrence of KIT, BRAF, and KRAS mutations in vitro. They found that presence of BRAF or KRAS mutation neutralized the impact of imatinib in KIT-positive tumors. Among the 64 KIT- and PDGFRA-positive sporadic patients in our series, no BRAF or KRAS mutations were identified, suggesting that co-occurrence of these mutations is likely to be rare in the northwestern Italian population and not a frequent cause of primary resistance to imatinib in KIT-positive GIST patients. However, further studies, including clinical follow-up data, in a larger mutation-positive cohort from the same population, are needed to corroborate this hypothesis.

**Acknowledgments** We appreciated the generous contribution and the excellent work of the colleagues at the Departments of Pathology at the Galliera, Sampiardarena, Savona, Pietra Ligure, Sanremo, and Imperia Hospitals.

## Appendix

Liguria GIST Unit, IRCCS AOU S. Martino-IST, Genoa, Italy

Participants:

Dr. Danila Comandini, Department of Medical Oncology

Prof. Franco De Cian, Department of Surgery, Unit of Oncologic Surgery

Dr. Luca Mastracci, Department of Anatomic Pathology

Prof. Giovanna Bianchi Scarrà, Laboratory of Genetics of Rare Hereditary Cancers

External collaborator:

Dr. Ennio Biscaldi, Department of Radiology, Galliera Hospital, Genova.

## References

1. Parfitt JR, Streutker CJ, Riddell RH, Driman DK. Gastrointestinal stromal tumors: a contemporary review. Pathol Res Pract. 2006;202:837–47.
2. Wardelman E, Pauls K, Mekelbach-Bruse S, Hrychyk A, Losen I, Hohenberger P, et al. Gastrointestinal stromal tumors carrying PDGFR alpha mutations occur preferentially in the stomach and exhibit an epithelioid or mixed phenotype. Verh Dtsch Ges Pathol. 2004;88:174–83.
3. Agaimy A, Terracciano LM, Dirnhofer S. V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRA wild-type gastrointestinal stromal tumours. J Clin Pathol. 2009;62:613–6.
4. Hostein I, Faur N, Primois C, Boury F, Denard J, Emile JF, et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol. 2010;133:141–8.
5. Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, 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 tumors expressing KIT. J Clin Oncol Off J Am Soc Clin Oncol. 2008;26:620–5.
6. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21:4342–9.
7. Joensuu H, De Matteo RP. The management of gastrointestinal stromal tumors: a model for targeted and multidisciplinary therapy of malignancy. Annu Rev Med. 2012;63:247–58.
8. Antonescu CR. The GIST paradigm: lessons for other kinase-driven cancers. J Pathol. 2011;223(2):251–61.
9. Miranda C, Nucifora M, Molinari F, Conca E, Anania MC, Bordoni A, et al. KRAS and BRAF mutations predict primary resistance to imatinib in gastrointestinal stromal tumors. Clin Cancer Res. 2012;18(6):1769–76.
10. Hostein I, Debiec-Rychter M, Olschwang S, Bringuier PP, Toffolati L, Gonzalez D, et al. A quality control program for mutation detection in KIT and PDGFRA in gastrointestinal stromal tumours. J Gastroenterol. 2011;46:586–94.
11. Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. Lab Invest. 2004;84:874–83.
12. Steigen SE, Eide TJ, Wasag B, Lasota J, Miettinen M. Mutations in gastrointestinal stromal tumors: a population-based study from Northern Norway. APMIS. 2007;115:289–98.
13. Bachet JB, Hostein I, Le Cesne A, Brahimi S, Beauchet A, Tabone-Eglinger S, et al. Prognosis and predictive value of KIT exon 11 deletion in GISTs. Br J Cancer. 2009;101:7–11.
14. Kotogianni-Katsarou K, Dimitriadis E, Lariou C, Kairi-Vassilatou E, Pandis N, Kondi-Paphiti A. KIT exon 11 codon 557/558 deletion/insertion mutations define a subset of gastrointestinal stromal tumors with malignant potential. World J Gastroenterol. 2008;14:1891–7.
15. Vila L, Liu H, Al-Quran SZ, Coco DP, Dong HJ, Liu C. Identification of c-kit gene mutations in primary adenoid cystic carcinoma of the salivary gland. Mod Pathol. 2009;22:1296–302.
16. Ezoe K, Holmes SA, Ho L, Bennett CP, Bolognia JL, Brueton L, et al. Novel mutations and deletions of the KIT (steel factor receptor) gene in human piebaldism. Am J Hum Genet. 1995;56:58–66.
17. Kuwahara Y, Hirata A, Miwa H, Munakata S, Ueda S, Kanakura Y, et al. Epstein-Barr virus associated B-cell lymphoma of brain developing in myelodysplastic syndrome with c-kit mutation (Try-557 → stop). Am J Hematol. 2000;65:234–8.
18. Antonescu CR, Besmer P, Guo T, Arkun K, Hom G, Koryotowski B, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res. 2005;11:4182–90.
19. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer. 2011;11:865–78.
20. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125:660–7.
21. Demetri GD. Targeting the molecular pathophysiology of gastrointestinal stromal tumors with imatinib. Mechanisms, successes, and challenges to rational drug development. Hematol Oncol Clin N Am. 2002;16:1115–24.
22. Adim SB, Filiz G, Kanat O, Yerci O. Simultaneous occurrence of synchronous and metachronous tumors with gastrointestinal stromal tumors. Bratisl Lek Listy. 2011;112:623–5.