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Original article

Focal progression in patients with gastrointestinal stromal tumors after initial response to imatinib mesylate: a three-center-based study of 38 patients

Salah-Eddin Al-Batran[1], Joerg Thomas Hartmann[2], Florian Heidel[3], Jan Stoehlmacher[4], Eva Wardelmann[5], Claudius Dechow[6], Markus Düx[6], Jacob Robert Izbicki[4], Thomas Kraus[7], Thomas Fischer[3], and Elke Jäger[1]

[1] Department of Hematology and Oncology, Krankenhaus Nordwest, Steinbacher Hohl 2-26, 60488 Frankfurt am Main, Germany
[2] Department of Medical Oncology, Hematology, Immunology, Rheumatology and Pulmology, South West Cancer Center, Eberhard-Karls-University, Tuebingen, Germany
[3] Third Medical Department, Johannes Gutenberg University, Mainz, Germany
[4] Department of Internal Medicine and Department of Surgery, University Hospital Eppendorf, Hamburg, Germany
[5] Department of Pathology, University of Bonn Medical Center, Bonn, Germany
[6] Department of Radiology, Krankenhaus Nordwest, Frankfurt, Germany
[7] Department of Surgery, Krankenhaus Nordwest, Frankfurt, Germany

Abstract

Background. **This study aimed to investigate the outcome of patients with advanced gastrointestinal stromal tumors (GISTs) exhibiting focal disease progression during imatinib therapy, treated by surgical resection and imatinib continuation.**

Methods. **A consecutive series of 38 patients with metastatic GISTs who underwent treatment with imatinib at our centers during a defined period of time was evaluated. Patients were evaluated for demographics including tumor-related features, initial response, disease recurrence, and salvage treatment modalities, and were classified as having either focal or generalized progression upon presentation prior to salvage therapy.**

Results. **After a median follow-up of 31.8 months, 25 of the 38 (65.8%) patients had progressed. Nine (36%) patients were classified as having focal and 16 (64%) as having generalized progression. Salvage therapies were: surgical resection and imatinib dose escalation in patients exhibiting focal progression and imatinib dose escalation alone in the majority of patients exhibiting generalized progression. Focal progression was associated with prolonged progression-free survival (PFS) and overall survival (OS) after salvage therapy as compared with generalized progression (median PFS and OS, 11.3 months and not attained, versus 2.5 and 22.8 months, respectively). Six-month PFS was 89% and 39% in patients exhibiting focal and generalized progression, respectively. *KIT* mutation analysis of controlled and progressive lesions was performed in 4 patients with focal progression. Secondary *KIT* mutations affected progressive lesions, whereas nonprogressive lesions harbored the original mutations only.**

Conclusion. **Patients with advanced GIST exhibiting focal disease progression during imatinib therapy may benefit from surgical resection and imatinib continuation. Imatinib resistance seems to be partial in these patients.**

Key words Focal · Limited · Generalized · Progression · Gastrointestinal · Stromal · Tumor · Imatinib

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignancy of the gastrointestinal tract [1]. GISTs express the tyrosine kinase receptor *KIT*, which is the protein product of the *KIT* protooncogene. GISTs are generally characterized by gain-of-function mutations of *KIT* [2]. These mutations result in the constitutive activation of *KIT* signaling and are the likely causal molecular events of GIST [3,4].

GISTs are completely resistant to conventional chemotherapy. Imatinib, a tyrosine kinase inhibitor active against *KIT* and platelet-derived growth factor receptor, has been shown to be highly effective in the treatment of advanced GIST. Clinical benefit was demonstrated in more than 80% of patients, resulting in a substantial improvement in the 2-year survival rate, from 26% to 76% [5,6]. Imatinib has, therefore, become the standard of care in patients with advanced GIST. However, imatinib is not curative and secondary resistance to imatinib often occurs within the first or second year of treatment [7]. In these patients, clinicians increase the dose of imatinib despite disease progression and, in addition, consider surgical resection or

Offprint requests to: S.-E. Al-Batran
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radiofrequency ablation in patients with focal imatinib resistance [8]. However, the role of local treatment in this setting has not been proven yet and additional research examining the phenomenon of focal progression is warranted.

Patients and methods

Patients

All patients who had started on imatinib treatment between June 2001 and December 2002 at three cancer centers were followed for a period of at least 30 months. Patients eligible for the retrospective analysis had histologically confirmed metastatic, unresectable GIST, measurable disease, and clinical staging done by computed tomography (CT) or magnetic resonance imaging (MRI). Participating centers had multidisciplinary teams experienced in sarcoma and gastrointestinal cancer management. The analysis was performed with the permission of the responsible ethics review board.

The medical records of all patients were reviewed. Demographic and baseline data at the initiation of imatinib treatment that were taken into consideration were: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor location, primary histopathology, organs involved in metastatic disease, and time between first diagnosis and the initiation of imatinib. Patients were regularly evaluated every 3 months for tumor response by the Response Evaluation Criteria in Solid Tumours (RECIST). The CT or MRI scans of the target areas were reviewed prior to imatinib initiation and every follow-up until first disease progression. The clinical follow-up was updated to May 2005 and checked, on a queries-based survey, by the central reviewer and the centers. Patients whose disease progressed were classified as: (a) having focal disease progression, defined as a progression (RECIST) of resectable tumor lesions within unresectable but actually nonprogressive disease manifestations or (b) having generalized disease progression (defined as the progression of unresectable tumor lesions). Patients considered for surgical debulking were defined as having generalized disease progression. The primary goal of surgery in patients with focal progression was to remove all sites of progressing disease.

Mutation analysis

Mutation analysis in exons 9, 11, 13, 14, and 17 of *KIT* was done as previously described [9]. Tumor tissue for DNA extraction was marked on slides stained with hematoxylin and eosin and microdissected from serial sections (10 μm). Total DNA was extracted after pretreatment with proteinase K and absorption on silica gel membranes (Qiagen, Hilden, Germany). Exon sequences were amplified by the use of intronic primers described previously [10]. Polymerase chain reaction (PCR) products were purified with Micro Spin columns (Amersham Biosciences, Freiburg, Germany). Bidirectional DNA sequencing of the complete exons and corresponding exon–intron boundaries was done with the Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Weiterstadt, Germany). Cycle sequencing products were precipitated with sodium acetate (3 mol/l) and analyzed on an ABI PRISM 310 capillary electrophoresis system (Applied Biosystems). All sequence alterations were confirmed by independent PCR amplification and sequencing to exclude PCR artefacts. Amplicon sequences were identified by database search [accession number, HSU63834; National Center for Biotechnology Information (NCBI) database, www.ncbi.nlm.nih.gov].

Statistical analysis and definition of progression-free intervals

Progression-free survival (PFS) and overall survival (OS) were determined according to Kaplan-Meier methods. PFS_1 was measured from the start of front-line imatinib therapy until progression of disease. PFS_2 was measured from the start of salvage therapy until second progression or death of any cause. OS was measured from the start of the front-line imatinib treatment until death of any cause.

Results

Patients

Thirty-eight patients were included at three cancer centers. The mean age of the patients at the initiation of imatinib was 58.4 years (range, 37 to 73 years) and the median ECOG performance status was 1 (range, 0 to 2). Twenty-one of the 38 patients were male; all patients had metastatic disease, with liver or peritoneal metastasis of spindle-cell histology as the most common site of involvement. Patient characteristics and treatment histories are listed in Table 1.

Initial response to imatinib

No patient had a complete response to the treatment. Twenty-eight of the 38 patients (73.7%; 95% confidence interval [CI], 59.7% to 87.7 %) had a partial response. Six patients (15.8%; 95% CI, 4.2% to 27.4%) had stable disease and 3 patients had progressive disease (7.9%; 95% CI, 0.8% to 20.3%). One patient (2.6%) was not evaluable for response (Table 2).

Table 1. Patient characteristics by subgroup

Characteristic	All patients $n = 38$ (%)	Focal progression $n = 9$ (%)	Generalized progression $n = 16$ (%)	No progression documented $n = 13$ (%)
Sex				
Male	21 (55.3)	4 (44.4)	8 (50)	9 (69.2)
Female	17 (44.7)	5 (55.6)	8 (50)	4 (30.8)
Age, years				
Mean	58.4			
Range, years	37–73			
30–49	8 (21.1)	2 (22.2)	3 (18.8)	3 (23.1)
50–69	23 (60.5)	7 (77.7)	11 (68.7)	5 (38.5)
70–79	7 (18.4)	0 —	2 (12.5)	5 (38.5)
ECOG performance status				
0	13 (34.2)	6 (66.6)	3 (18.8)	4 (30.8)
1	18 (47.4)	3 (33.3)	9 (56.2)	6 (46.2)
2	7 (18.4)	0 —	4 (25)	3 (23.1)
Primary site of disease				
Gastric	11 (28.9)	1 (11.1)	6 (37.5)	4 (30.8)
Small bowel	8 (21.1)	2 (22.2)	3 (18.8)	3 (23.1)
Colon/rectal	2 (5.3)	1 (11.1)	0 —	1 (7.7)
Other abdominal[a]	12 (31.6)	4 (44.4)	4 (25)	4 (30.8)
Retroperitoneal	3 (7.9)	0 —	3 (18.8)	0 —
Unknown	2 (5.3)	1 (11.1)	0 —	1 (7.7)
Disease status at imatinib initiation				
Initial diagnosis	19 (50)	2 (22.2)	11 (68.8)	6 (46.2)
Recurrent	19 (50)	7 (77.8)	5 (31.2)	7 (53.8)
Interval since initial diagnosis, months				
<12	21 (55.3)	2 (22.2)	12 (75)	7 (53.8)
12–24	11 (28.9)	1 (11.1)	4 (25)	6 (46.2)
>24	6 (15.8)	6 (66.7)	0 —	0 —
No. of organs involved				
1	4 (10.5)	0 —	1 (6.3)	3 (23.1)
2	18 (47.4)	4 (44.4)	9 (56.2)	5 (38.5)
3	9 (23.7)	3 (33.3)	3 (18.8)	3 (23.1)
>3	7 (18.4)	2 (22.2)	3 (18.8)	2 (15.4)
Site of disease				
Liver	27 (71.1)	5 (55.5)	13 (81.3)	9 (69.2)
Peritoneum	20 (52.6)	5 (55.6)	12 (75)	3 (23.1)
Gastric	11 (28.9)	1 (11.1)	6 (37.5)	4 (30.8)
Small bowel	9 (23.7)	2 (22.2)	3 (18.8)	4 (30.8)
Colon and rectum	6 (15.8)	2 (22.2)	0 —	1 (7.7)
Others[b]	17 (44.7)	5 (55.5)	5 (31.2)	8 (61.5)
Previous treatment (prior to imatinib)				
Surgery	27 (71.1)	9 (100)	9 (56.3)	9 (69.2)
Chemotherapy	8 (21.1)	4 (44.4)	3 (18.8)	1 (7.7)
Radiotherapy	2 (5.3)	2 (22.2)	0 —	0 —

[a] Including peritoneal and omental disease
[b] Pancreas, 4 patients; retroperitoneum, 3 patients; abdominal lymph nodes, 3 patients; spleen, 3 patients; kidney, 2 patients; esophagus, 2 patients; prostate, 1 patient; ovary, 1 patient; lung, 1 patient

Progression and survival

All 38 patients were included in the survival analysis. The median follow-up time was 31.8 months (range, 2.6 to 46.3 months) for the entire group and 37.8 months (range, 31.4 to 46.3 months) in surviving patients. At the time of analysis, 25 of the 38 (65.8%) patients had progressed. Two of the 38 (5.3%) patients died without documented disease progression and 11 (28.9%) patients were still responding. The overall median PFS_1 was 18.9 months (range, 1 to 43.5+ months), with the median OS not yet reached (Fig. 1). Nine of the 25 (36%; CI, 17.2% to 54.8%) progressions were classified as focal and 16 (64%; CI, 45.2% to 82.8%) as generalized. Early resistance to imatinib (within 3 months) [10] occurred in 6 of the 25 (24%) patients (focal, 22.2%; generalized, 25%).

Surgical resection was performed immediately in 6 of the 9 patients exhibiting focal progression and after imatinib dose escalation had failed to stop disease pro-

Table 2. Initial response to imatinib by subgroup

Best response	All patients $n = 38$ (%)	Focal progression $n = 9$ (%)	Generalized progression $n = 16$ (%)	No progression documented $n = 13$ (%)
CR	0 —	0 —	0 —	0 —
PR	28 (73.7)	6 (66.7)	12 (75)	10 (76.9)
SD	6 (15.8)	1 (11.1)	2 (12.5)	3 (23.1)
PD	3 (7.9)	1 (11.1)	2 (12.5)	— —
NE	1 (2.6)	1 (11.1)	0 —	0 —
Early imatinib resistance[a]	6 (15.8)	2 (22.2)	4 (25)	— —

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable
[a] Defined as progression within 3 months after initiation of imatinib treatment [11]

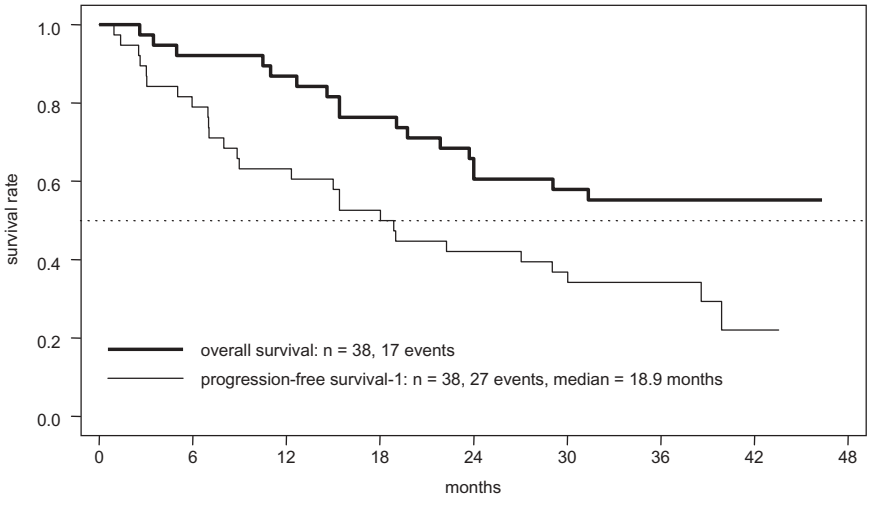

Fig. 1. Overall and progression-free survival-1 ($n = 38$)

gression in the other 3 patients. Complete resection of macroscopic (progressive) disease was achieved in all patients with focal disease progression. Surgical procedures performed were: bowel segment resection (5 patients), hepatic resection (1 patient), hepatic resection and bowel segment resection (1 patient), resection of abdominal wall tumor (1 patient), and resection of retroperitoneal tumor (1 patient). The starting dose of imatinib was 400 mg per day in all patients. All patients with focal progression continued on imatinib after surgical resection (maximum imatinib dose, 600 mg in 1 patient and 800 mg in 8 patients). The dose of imatinib was escalated to a maximum of 800 mg per day in 13 and discontinued in 2 of the 16 patients who had generalized disease progression, and there was no information available on further imatinib dose for the remaining patient in this group. Two patients with generalized progression underwent tumor reduction surgery (resection of pelvic tumors).

The median PFS_2 in patients exhibiting focal progression ($n = 9$) was 11.3 months (range, 6.7–23.2+ months). The corresponding 6- and 12-month PFS_2 rates were 89% and 40%, respectively. The median OS for this patient group has not been reached after a median follow-up time of 31.4 months (range, 10.5 to 46.3 months). In contrast, the median PFS_2 in patients exhibiting generalized progression was 2.5 months (range, 0.7 to 17.7 months), and the corresponding 6- and 12-month PFS_2 rates were 39% and 32%, respectively. The median OS for patients with generalized progression was 22.8 months (range, 2.6 to 45.1 months). PFS and OS are illustrated for the entire group and depending on the type of progression in Figs. 1–4.

There were no remarkable differences in the initial response to imatinib (focal, 66.7%; generalized, 75%) or in median PFS_1 (focal, 8.8 months; generalized, 8.0 months) between the two groups of patients, as shown in Fig. 2 and Table 2.

Mutation analysis

Intraoperative tumor biopsies were taken from four patients with focal progression. Mutation analysis of the primary tumor (archival material) and the

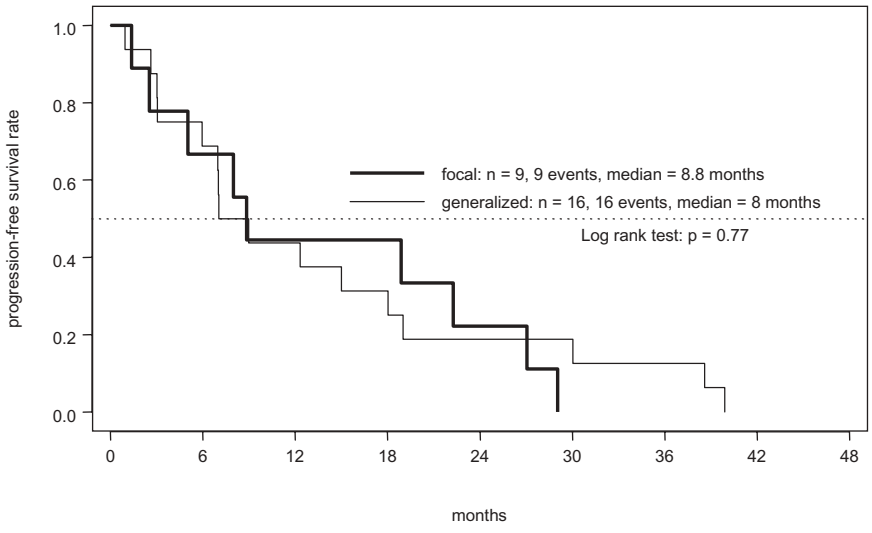

Fig. 2. Progression-free survival-1 (time from the start of front-line imatinib until progression of disease) in patients with focal versus generalized progression

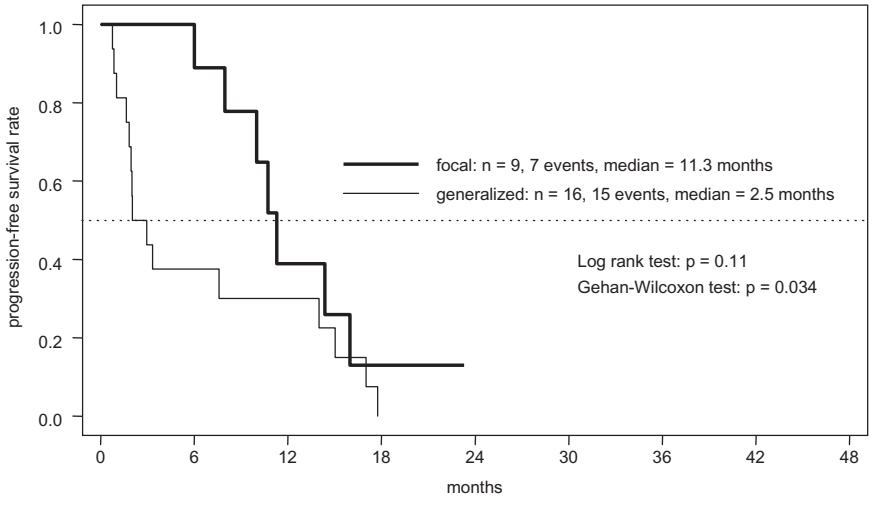

Fig. 3. Progression-free survival-2 (time from the start of salvage therapy until second progression or death of any cause) in patients with focal versus generalized progression

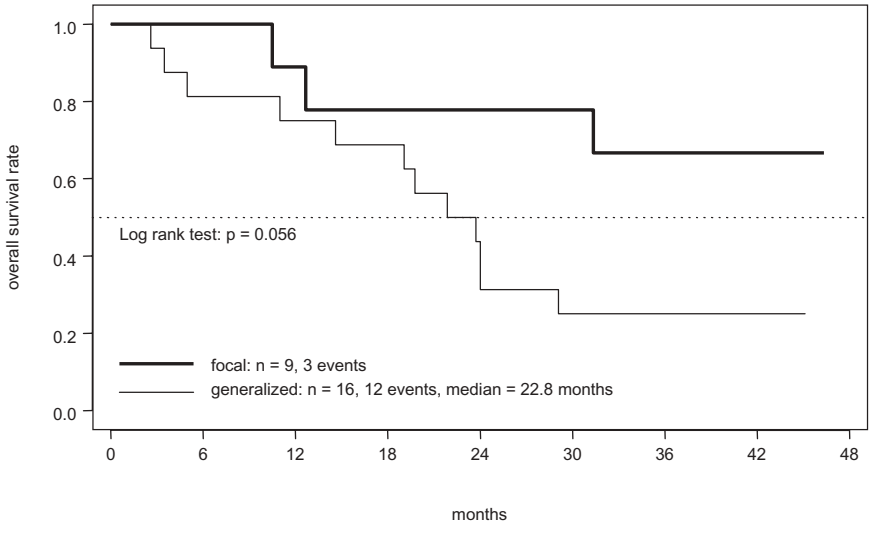

Fig. 4. Overall survival in patients with focal versus generalized progression

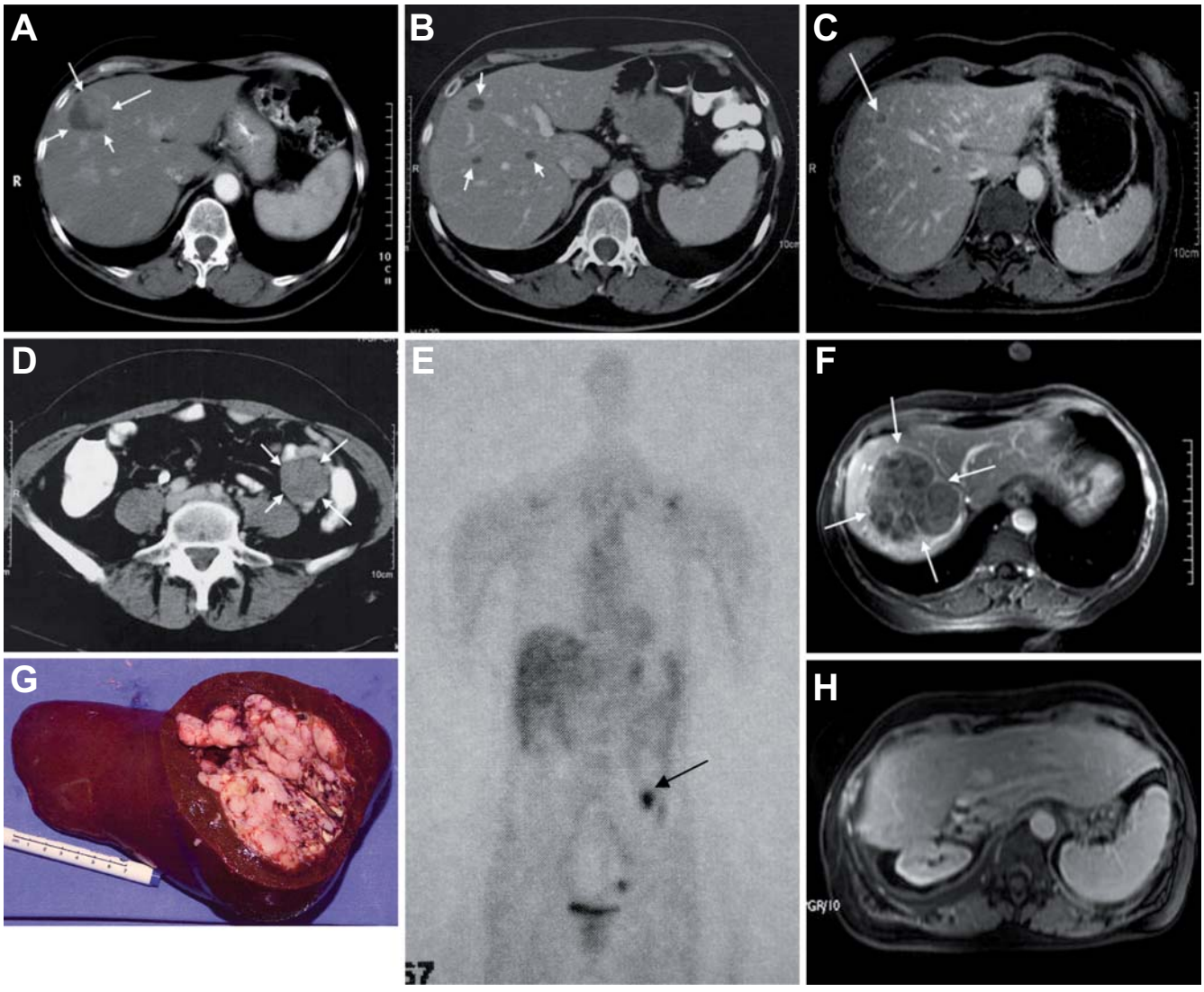

Fig. 5A–H. Serial imaging in a 56-year old female patient with a gastrointestinal stromal tumor (GIST), primarily located in the small bowel and metastatic to peritoneum and liver. **A** computed tomography (CT) scan of the liver prior to imatinib treatment shows multiple active lesions (*arrows*). **B** and **C** CT scans show partial remission after 3 and 9 months of imatinib treatment (*arrows*). **D** CT scan shows progressive mass in the left lower abdomen (*arrows*) after 17 months of treatment (defined as focal progression). **E** 18F-Fluoro-deoxyglucose-positron emission tomography (FDG-PET) scan confirms increased uptake only in the growing lesion (*arrow*). The mass was surgically removed, and intraoperative biopsies of several mesenteric (see Table 3 for details of the lesions) and peritoneal (nonprogressive) lesions were taken. **F** Sixteen months after the surgical removal of the mass, magnetic resonance imaging (MRI) scan demonstrated rapid progression in the right liver (defined as focal progression). **G** Extended right hepatic resection achieved complete removal of the progressive mass (see Table 3 for details of the mass). **H** MRI done 3 months after resection confirmed controlled disease

nonprogressive and progressive lesions was performed. In addition to the original mutations (V560D, W557_K558del, L576P, and W557_K558del), all the progressive lesions that were evaluated harbored secondary *KIT* mutations–T670E, V654A, N822Y, and V654A–that were previously described to be associated with imatinib resistance [11]. On the other hand, biopsies of the nonprogressive lesions harbored the original mutations only. Details of the clinical management and pathological and molecular findings of an index patient with focal progression are shown in Fig. 5 and Table 3.

Discussion

The present analysis shows that focal disease progression occurred in a significant proportion of our GIST patients. Twenty-four percent of our patients developed

Table 3. Pathological and molecular findings in nonprogressive and progressive lesions of the index patient whose findings are shown in Fig. 5

Test	Mesenteric (nonprogressive) lesions	Progressive lesion–jejunum[a]	Progressive lesion–liver[b]
Histopathology	Strongly regressive tumors with scattered vital cells present in a myxohyaline stroma	Cell-rich nodules with highly polymorphous nuclei, onion skin-like arrangement	Interlacing fascicles of spindle cells arranged in a whorled pattern. Highly polymorphous nuclei
Ki-67	<1%	30%	>30%
CD34[c]	–	+++	++
BCL2[c]	–	–	ND
PDGFR-alpha[c]	–/+	+/+++ Inhomogeneous	ND
c-kit[c]	–	+/++++ Inhomogeneous	+++
DNA sequencing			
c-Kit Exon 9	Wild type	Wild type	Wild type
c-Kit Exon 11	Point mutation V560D	Point mutation V560D	Point mutation V560D
c-Kit Exon 13	Wild type	Wild type	Point mutation V654A
c-Kit Exon 14	Wild type	Point mutation T670E	Wild type
c-Kit Exon 15	Wild type	Wild type	Wild type
c-Kit Exon 17	Wild type	Wild type	Wild type

ND, not done
[a] Fig. 5D
[b] Fig. 5F,G
[c] Immunohistochemistry was evaluated using a semiquantitative scoring system (–, negative; +, mild; ++, moderate; +++, strong)

focal progression that was treated by surgical resection and imatinib continuation. Furthermore, patients exhibiting focal disease progression appeared to have a better clinical outcome as compared to patients exhibiting generalized disease progression. The median PFS_2 and corresponding 6- and 12-month PFS rates were 11.3 months, 89%, and 40%, respectively, in patients with focal disease progression versus 2.5 months, 39%, and 32%, respectively, in patients with generalized disease progression (log-rank test, $P = 0.11$; Wilcoxon test, $P = 0.034$). There was also a statistical trend to prolonged OS in patients exhibiting focal progression (log rank test, $P = 0.056$). These observations are in line with the results of a recent study indicating that GIST patients exhibiting focal disease progression appeared to have prolonged overall survival as compared with patients exhibiting "generalized" progression after surgical resection was performed in both groups of patients [12].

Baseline characteristics and overall clinical development in our patient population did not differ from those reported in large prospective studies [13,14]. Particularly, the rate of disease control (89.5%) with imatinib and median progression-free survival (18.9 months) were within the expected ranges. In our series, patients with focal progression did not seem to differ from others in term of imatinib responsiveness (initial response to imatinib, early or late resistance, and PFS_1 were comparable between the two groups).

Patients with generalized progression in our study had median and 12-month PFS_2 of 2.5 months and 32%, respectively, after the dose escalation of imatinib. These findings appear to be consistent with results known from the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG) trial. In that trial, patients ($n = 946$) with advanced GIST were randomized to receive imatinib 400 or 800 mg daily. Patients randomized to low-dose imatinib could crossover to high-dose upon progression. The median and 12-month PFS after crossover were 2.7 months and 18%, respectively [15].

Recent reports have supported the view that acquired imatinib resistance is caused by secondary resistance mutations of *KIT* [16–18]. In one study, such mutations were found in 7 of 15 (46%) patients who progressed after the initial response to imatinib; most of the mutations were located in exon 17 of the *KIT* gene [11]. We detected secondary *KIT* mutations in the growing masses but not in the nonprogressive disease manifestations of all four evaluated patients exhibiting focal progression. Pathological and immunohistochemical findings confirmed active disease in the lesions that were found to be progressive on imaging and harbored the secondary mutations. All secondary mutations detected in our patients have been previously described. However, we showed that progressive lesions harboring secondary mutations did coexist synchronously with nonprogressive lesions harboring the original mutation only in the same patient. This supports the view that focal progressions on imatinib treatment may occur due to the localized clonal evolution of tumor cells harboring secondary mutations at one or a few disease sites. Generalized progressions, on the other hand, may be

related to the spreading of genetically unstable clones, the simultaneous occurrence of multiple secondary mutations [18], unfavorable primary *KIT* mutations, or other mechanisms of drug resistance unrelated to *KIT* mutations. Further studies are warranted to investigate this speculation at clinical and molecular levels.

In conclusion, the results of our study add to the body of data supporting the view that imatinib resistance seems to be partial in a subset of GIST patients. In these patients, the use of surgical approaches in addition to imatinib continuation may result in a favorable clinical outcome.

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