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Clinicopathological and Molecular Characterization of Metastatic Gastrointestinal Stromal Tumors with Prolonged Benefit to Frontline Imatinib

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. c-KIT • Gastrointestinal stromal tumor • Imatinib mesylate • Long-term

Abstract

Background. Oncogenic KIT/PDGFRA signaling inhibition with imatinib achieves disease control in most patients with advanced/metastatic gastrointestinal stromal tumor (GIST), but resistance eventually develops after 20–24 months. Notably, a small subset of these patients obtain durable benefit from imatinib therapy.

Methods. We analyzed clinical, pathological, and molecular characteristics and long-term outcomes in patients with metastatic GIST treated with continuous daily dosing of frontline imatinib in a cohort of patients benefiting for ≥5 years. A control group was obtained from the national Spanish Group for Sarcoma Research database and used as comparator.

Results. Sixty-four imatinib long-term responders (LTRs) and 70 control cases were identified. Compared with controls, LTRs at baseline had better performance status (PS) 0–1 (100% vs. 81%), lower mitotic count (median, 8 vs. 15), and tumor burden (number of metastases, 3 vs. 7). *KIT* exon 11 was the only region found mutated in LTRs. LTRs achieved 34% complete responses and a median progression-free survival of 11 years, compared with 4% and 2 years, respectively, in the control cohort. Prognostic factors that independently predicted long-term benefit with imatinib were PS, number of metastases prior to imatinib, and response to imatinib. Fifteen LTR patients developed new side effects attributable to imatinib after ≥5 years of continuous treatment. No resistance mutations were found in metastatic samples from three patients progressing on imatinib.

Conclusion. GISTs in LTRs are a distinctive entity with less aggressive behavior and marked sensitivity to KIT inhibition. Patients reaching 5 or more years on imatinib have a higher chance of remaining progression free over time. ***The Oncologist*** 2019;24:680–687

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Implications for Practice: This work demonstrates that clinical and inherent tumor characteristics define a subset of patients with gastrointestinal stromal tumor (GIST) with increased likelihood to achieve durable response to first-line imatinib therapy. Patients reaching ≥5 years on imatinib have a greater chance of remaining progression free over time, although the disease is unlikely to be cured. Imatinib is well tolerated for >5 years, and emergent toxicities are overall manageable. Resistance to imatinib emerging in patients with GISTs after long-term imatinib treatment does not involve polyclonal expansion of KIT secondary mutations.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignant neoplasm [1], with a population-based incidence rate of 1.1–1.2 cases per 100,000 per year [1,2]. GIST was recognized as a distinctive entity after the seminal discovery of gain-of-function mutations in *KIT* and *PDGFRA* receptor tyrosine kinases (RTKs), which are present in 85%–90% of GISTs [3,4]. This addiction to oncogenic KIT/PDGFRA signaling explains the profound effect of targeted inhibition of these RTKs with small molecules [5].

First-line imatinib mesylate was approved after the demonstration of sustained response in the landmark B2222 phase II trial [6]. In this study, 54% of patients with metastatic GIST achieved response, and 28% achieved stable disease (SD). A 5-year follow-up of this study showed a median progression free-survival (PFS) of 24 months and an estimated median overall survival (OS) of 57 months [7]. These results were further supported by two larger, randomized, international phase III trials in which more than 1,500 patients with metastatic GIST were treated with imatinib [8,9]. Unless uncommon significant toxicities occur, continuous imatinib therapy is advised because interruption results invariably in disease progression [10].

Although the vast majority of patients with metastatic GIST show sustained benefit from imatinib, disease progression typically occurs within 20–24 months after treatment initiation because of the polyclonal expansion of subclones harboring KIT secondary mutations [11,12]. Remarkably, a subset of patients with metastatic GIST achieve long-term disease control with first-line imatinib. In the B2222 study, approximately 30% of the patients remained progression-free after 5 years on continuous imatinib treatment [7]. Recent updates from the two phase III trials reported a 10-year PFS estimate of 7%–9%, therefore highlighting that a subgroup of patients with metastatic GIST are exquisitely sensitive to KIT/PDGFRA signaling inhibition with imatinib [13,14].

In the current study, we aimed to identify distinctive clinicopathological and molecular features in long-term responders (LTRs) to imatinib treatment in comparison with patients with GIST reaching the usual median PFS, and to provide further clinical insights from this subgroup collected during the long-term follow-up.

Subjects, Materials, and Methods

Patient Selection

We conducted a retrospective survey among sarcoma referral centers in Spain with experience in conducting clinical studies in sarcoma and/or GIST. All the investigators were members of the Spanish Group for Sarcoma Research (GEIS). Medical records from LTR patients with GIST were retrospectively collected in an electronic case report form between September 2016 and April 2017. LTRs with GIST were defined as follows: patients ≥18 years old with a histologically proven, unresectable, and/or metastatic GIST treated with continuous imatinib at any dose for ≥5 years. Patients with GIST with treatment interruption of ≥1 month and/or surgical resection of disease while on imatinib were not recruited in order to capture the true impact of imatinib on long-term outcomes.

GIST control cases—patients who were also treated with imatinib for unresectable and/or metastatic disease, but for <5 years—were selected from the GEIS GIST database, which includes clinical, pathological, molecular, and follow-up data from 1,346 patients with GIST [15]. The final subset of control cases used for this study was selected following the above criteria applied to LTRs with GIST. LTRs identified within the GEIS GIST database were transferred to the LTR cohort for the analysis. This study was approved by the institutional review board of each participating center.

Pathology

Available tumor tissue was mandatory in all LTR GIST cases for central review at Vall d'Hebron University Hospital by an expert GIST pathologist (S.L.). Sections of formalin-fixed paraffin-embedded (FFPE) tissue (3 μm) were used for conventional hematoxylin and eosin staining and c-KIT immunostaining (A-4502, polyclonal, 1:400 dilution; DAKO, Copenhagen, Denmark). Immunohistochemistry was performed as described previously [16].

Genotyping

The presence of *KIT* mutations in exons 9, 11, 13, and 17 and *PDGFRA* mutations in exons 12 and 18 were assessed in FFPE samples from LTR cases as previously reported [3,17].

Next-Generation Sequencing

We used amplicon-based next-generation sequencing (NGS) technology (MiSeq platform; Illumina, San Diego, CA) for the detection of resistance mutations in FFPE samples from imatinib-progressing tumor samples. To this end, we ran the Amplicon-seq VHIO-card V2 panel of over 800 primer pairs targeting frequent mutations in oncogenes plus several tumor suppressors, totaling 61 genes. The average sequencing depth was ×1,000. Mutations were called at a minimum minor allele frequency of 3%. Analyses were performed as described previously [18].

Statistical Analysis

The cutoff date for statistical analysis of baseline demographic data and clinical outcome was April 30, 2017. Data were extracted from individual patients' files and analyzed. All centers conducted routine follow-up imaging studies at 3-month intervals. Response was assessed per-investigator using RECIST version 1.0.

Descriptive statistics were calculated for baseline characteristics for each group and compared using parametric (Student's *t*), nonparametric (Wilcoxon), or chi-square tests depending on each variable. PFS and OS curves were drawn according to the Kaplan-Meier method and compared using the log-rank test. Factors included in the univariate logistic regression model were age, sex, performance status (PS), primary tumor size, primary disease site, mitotic count, tumor rupture, type of mutation, time from diagnosis to metastatic relapse, number of metastases prior to imatinib treatment, and response to imatinib. Confounding and effect-modification variables were studied by multivariate analysis. All *p* values reported are two-tailed, and statistical significance was defined at $p < .05$. R version 3.3.0 (Vienna, Austria) was used for the statistical analysis.

Results

Clinical and Pathological Characteristics

Sixty-four consecutive LTRs with GIST and 70 GIST control cases were included in this study. Patients' baseline characteristics are detailed in Table 1. More patients in the LTR group had PS 0–1 compared with the control group ($p = .001$). For those patients with localized disease, there was a nonsignificant trend toward later metastatic relapse in LTRs (median, 2.4 years; range, 0.2–13) compared with controls (median, 1.9 years; range, 0.1–13; $p = .302$). Additionally, LTRs had a significantly lower burden of disease—measured as mean number of metastatic lesions—before starting first-line imatinib (mean, 3.2; standard deviation, 2.2) in contrast to controls (7.6; standard deviation, 4.8; $p < .001$). Metastatic locations did not differ between groups ($p = .451$) and followed the typical metastatic pattern in GIST.

Primary GIST tumors at the time of diagnosis did not differ in known risk factors for tumor relapse such as tumor size ($p = .767$), location ($p = .221$), or tumor rupture ($p = .823$). Tumor proliferation, evaluated as mitotic count per 50 high-power fields, although high in both groups, was significantly lower in LTRs (median, 8; range, 0–99) compared with control GIST cases (median, 15; range, 0–157; $p = .004$). This did not affect the distribution of patients with localized GIST across the modified National Institutes of Health consensus criteria; most of them fell within the high-risk category regardless of the long-term impact of imatinib ($p = .341$). Histological examination of the tumors (phenotype and c-KIT expression) did not yield significant differences (Table 1).

Genotype Analysis

KIT/PDGFRA mutations were identified in 49 out of 52 analyzed samples (94%) from LTRs with GIST and in 38 out of 50 control cases (71%; $p = .03$; Table 2). Unlike in control cases, *KIT* exon 11 was the only region from the *KIT* gene found mutated in LTRs ($p = .081$). The type of *KIT* exon 11 mutations (deletion vs. insertion/duplication vs. point mutation) and the distribution of codons affected were similar among both groups (supplemental online Fig. 1). Mutations affecting critical *KIT* exon 11 codons 557 and/or 558 were also similar across LTR and control cohorts ($p = .942$).

Efficacy of Imatinib Therapy for Metastatic Disease

Median follow-up time in LTR and control cohorts was 11.3 and 4 years, respectively. At the time of the cutoff, 67% ($n = 43$) of LTRs and 25% ($n = 18$) of control patients were still on imatinib treatment ($p < .001$). Patients with GIST that were ≥5 years on continuous imatinib for unresectable/metastatic disease had a median PFS of 10.6 years (95% CI 9.8–not reached), which was significantly superior to that of patients in the control cohort (2 years; 95% CI, 1.6–2.9; $p < .001$; Fig. 1). Likewise, OS was lower in the control cohort (4 years; 95% CI, 2.6–4.3) than in LTR ($p < .001$), in which the low number of events (6/63, compared with 38/70 in controls) yielded a non-reached result.

Sixty LTRs and 65 control patients were evaluable for response. Notably, tumor shrinkage was significantly more common in LTR, as 37% achieved complete response (CR) compared with 5% in control patients ($p < .001$; Table 1). Likewise, overall response rate (CR + partial response [PR]) was 68% in LTRs and 49% in control patients ($p = .047$).

More patients in the control arm (37%) were shifted to imatinib 800 mg per day at the time of disease progression than in LTR (19%; $p = .03$). However, the benefit of dose increase was comparable between both groups in terms of median PFS and response rate (data not shown).

Clinicopathological and Molecular Features Predictive of Long-Term Benefit with Imatinib

The following prognostic factors were identified by univariate analysis as predictive of long-term benefit with imatinib: PS, mitotic count, mutational status (*KIT* exon 11 vs. other), number of metastases prior to imatinib, and response (CR vs. other). In the logistic regression multivariate model, baseline characteristics that predicted independently long-term benefit with imatinib were PS, number of metastases prior to imatinib, and response to imatinib (Table 3).

Emerging Toxicities in LTRs

Data from emerging toxicities after ≥5 years on treatment were collected in 58 LTRs. In total, 15 LTRs (26%) developed 20 new side effects attributable to imatinib, which are detailed in supplemental online Table 1. Most toxicities were grade 1 or 2. The four grade 3 toxicities recorded included bilateral osteonecrosis of femoral head (one), edema/effusion (two), and macrocytic anemia (one). Toxicities were nonetheless manageable, and only four patients withdrew imatinib therapy because of recurrent grade 3 edema/effusion (two cases) and limiting recurrent anemia (two cases).

Long-Term Follow-Up

Six LTRs withdrew from imatinib and remained on follow-up without any treatment. The median time on imatinib

Table 1. Clinical and pathological features prior to imatinib initiation

Characteristics	Long-term responders (*n* = 64), *n* (%)	Control cohort (*n* = 70), *n* (%)	*p* value
Age, yr			
Median	62	63	.313
<40	9 (14)	4 (6)	
40–60	22 (34)	26 (37)	
>60	33 (52)	39 (57)	
Sex			.509
Male	38 (59)	36 (52)	
Female	26 (41)	33 (48)	
ECOG PS			.001
0	23 (39)	4 (6)	
1	36 (61)	48 (75)	
2	0 (0)	11 (17)	
3	0 (0)	1 (2)	
Disease status			.622
Localized	42 (66)	42 (60)	
Metastatic	22 (34)	28 (40)	
Metastatic relapse, y	2.4	1.9	.302
Number of metastases	3	8	<.001
Metastatic location			.451
Peritoneum	27 (42)	21 (38)	
Liver	22 (34)	18 (32)	
Liver and peritoneum	7 (11)	12 (21)	
Other	8 (13)	5 (9)	
Tumor size, cm			
Median	9.0	10.0	.767
<5	10 (17)	10 (17)	
5–10	21 (37)	30 (46)	
>10	28 (46)	24 (37)	
Tumor location			.221
Stomach	23 (36)	22 (32)	
Small bowel	26 (41)	38 (54)	
Other	15 (23)	10 (14)	
Mitotic count (per 50 HPF)			.004
Median	8.0	14.5	
<5	26 (45)	17 (30)	
5–10	12 (21)	6 (11)	
>10	20 (34)	33 (59)	
Tumor rupture			.823
Yes	6 (9)	9 (13)	
No	46 (72)	52 (74)	
Unknown	12 (19)	9 (13)	
Risk category			.341
Low	6 (17)	3 (9)	
Intermediate	2 (6)	1 (2)	
High	27 (77)	31 (89)	
Phenotype			.792
Fusiform	38 (59)	36 (51)	
Epithelial	10 (16)	9 (13)	
Mixed	11 (17)	14 (20)	
Unevaluable	5 (8)	11 (16)	
c-KIT immunostain			.201
Positive	61 (95)	59 (84)	
Negative	1 (2)	5 (7)	
Unevaluable	2 (3)	6 (9)	
Best response			<.001
CR	22 (34)	3 (4)	
PR	19 (30)	29 (41)	
SD	19 (30)	20 (29)	
PD	0 (0)	13 (19)	
Unknown	4 (6)	5 (7)	

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HPF, high-power field; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. *KIT* and *PDGFRA* genotype

Characteristics	Long-term responders (*n* = 64), *n* (%)	Control cohort (*n* = 70), *n* (%)	*p* value
KIT mutation	46 (72)	36 (51)	.03
Exon 9	0 (0)	2 (3)	
Exon 11	46 (72)	33 (47)	
Exon 13	0	1 (1)	
Exon 17	0	0 (0)	
PDGFRA mutation	3 (4.5)	2 (3)	
Exon 12	1 (1.5)	0	
Exon 18	2 (3)	2 (3)	
KIT/PDGFRA WT	3 (4.5)	12 (17)	
Unknown	12 (19)	20 (29)	
Type of *KIT* exon 11 mutation			.677
Deletion	33 (72)	21 (81)	
Insertion/duplication	3 (7)	1 (4)	
Point mutation	10 (21)	4 (15)	
KIT exon 11 557/558 involvement			.942
Yes	28 (62)	18 (60)	
No	17 (38)	12 (40)	

Abbreviation: WT, wild-type.

before withdrawal was 8 years (range, 5.3–10.4). Four patients achieved CR, one achieved PR, and one achieved SD. After a median time of 1.7 years on surveillance (range, 0.6–4), only one patient with CR progressed after 2.3 years

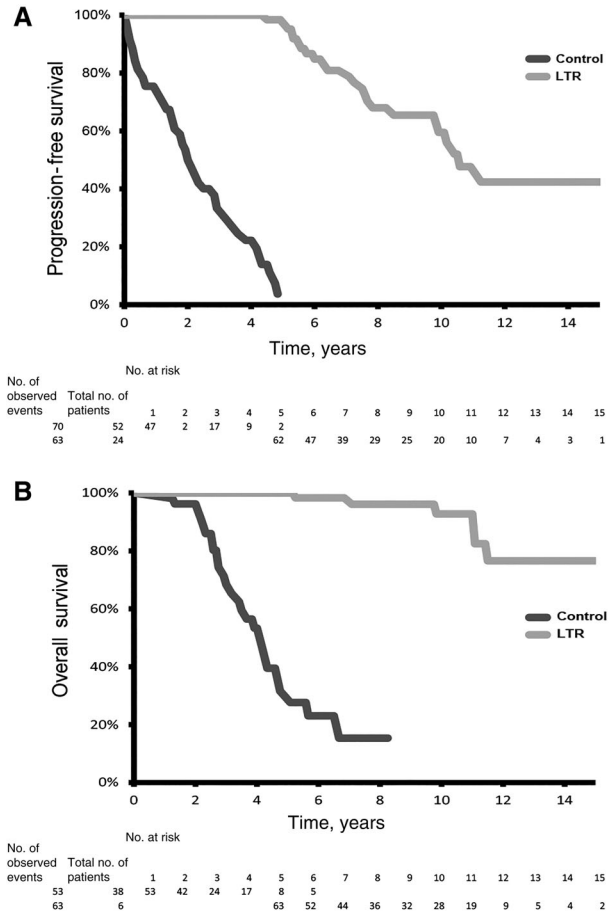

Figure 1. Kaplan-Meier plots showing progression-free survival **(A)** and overall survival **(B)**.
Abbreviation: LTRs, long-term responders.

of follow-up. This patient arrived in very poor condition at the emergency department and died shortly thereafter.

Eleven LTR patients (17%) progressed after ≥5 years on continuous imatinib. Tumor samples were obtained from three patients at the time of progression, and mutational status was analyzed by NGS. Primary mutations were consistent to those from baseline samples (case 1, *KIT* exon 11 p.N567_T574del; case 30, *KIT* exon 11 p.V559_L576delinsV; case 53, *PDGFRA* exon 18 p.D842_H845del). Surprisingly, no resistance mutations in the 61 studied genes [18], including *KIT/PDGFRA*, were identified. Interestingly, case 53 showed a shift in tumor phenotype, as the primary tumor was predominantly fusocelullar with an intense and diffuse c-KIT staining pattern, whereas the lesion progressing after ≥5 years was epithelioid and with a weak c-KIT immunostaining (Fig. 2), clearly indicative of an underlying unidentified mechanism of resistance.

Discussion

Although imatinib substantially improves survival in most patients with advanced/metastatic GIST, emergence of resistance often develops after 2 years on imatinib [6,8,9]. Notably, longer follow-up recently identified a subset of long-term survivors and progression-free survivors. Specifically, approximately one third of the patients remained progression-free after 5 years [7], and 7%–9% after 10 years of continuous imatinib therapy [13,14]. Our series focuses on patients with unresectable/metastatic GIST with durable benefit (≥5 years) from first-line imatinib, thereby confirming and expanding the current wealth of clinicopathological knowledge in this subset of patients reported in recent trial updates [13,14] and also providing novel prognostic, molecular, and follow-up data.

Herein we show that LTRs with GIST have distinctive clinicopathological and molecular features, compared with patients reaching the typical benefit with imatinib: better PS at diagnosis, decreased primary tumor cell proliferation, tendency toward later relapse, diminished capability to form metastases, predominance of *KIT* exon 11 mutations, and increased likelihood of tumor response. Three of these characteristics (PS, tumor burden, response to imatinib) were also found to be independent predictors of durable response with imatinib. An update from the European Organization for Research and Treatment of Cancer phase

Table 3. Prognosis factors predictive of long-term benefit with imatinib

Characteristics	OR (95% CI)	Univariate *p* value	OR (95% CI)	Multivariate *p* value
Age	0.98 (0.97–1)	.099		
Sex, female	0.75 (0.38–1.48)	.404		
ECOG PS	0.1 (0.03–0.33)	<.001	0.04 (0.01–0.55)	.015
Tumor size	1.01 (0.95–1.07)	.765		
Location[a]	0.82 (0.4–1.68)	.581		
Mitotic count	0.98 (0.96–0.99)	.02		
Tumor rupture	0.75 (0.25–2.28)	.616		
Mutation[b]	0.35 (0.17–0.72)	.004		
Metastatic relapse	1.01 (0.99–1.02)	.379		
No. of metastases	0.66 (0.55–0.79)	<.001	0.6 (0.42–0.86)	.005
Response[c]	0.08 (0.02–0.30)	<.001	0.04 (0–0.42)	.007

[a]Small bowel versus other.
[b]*KIT* exon 11 versus other.
[c]Complete response versus other.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; OR, odds ratio.

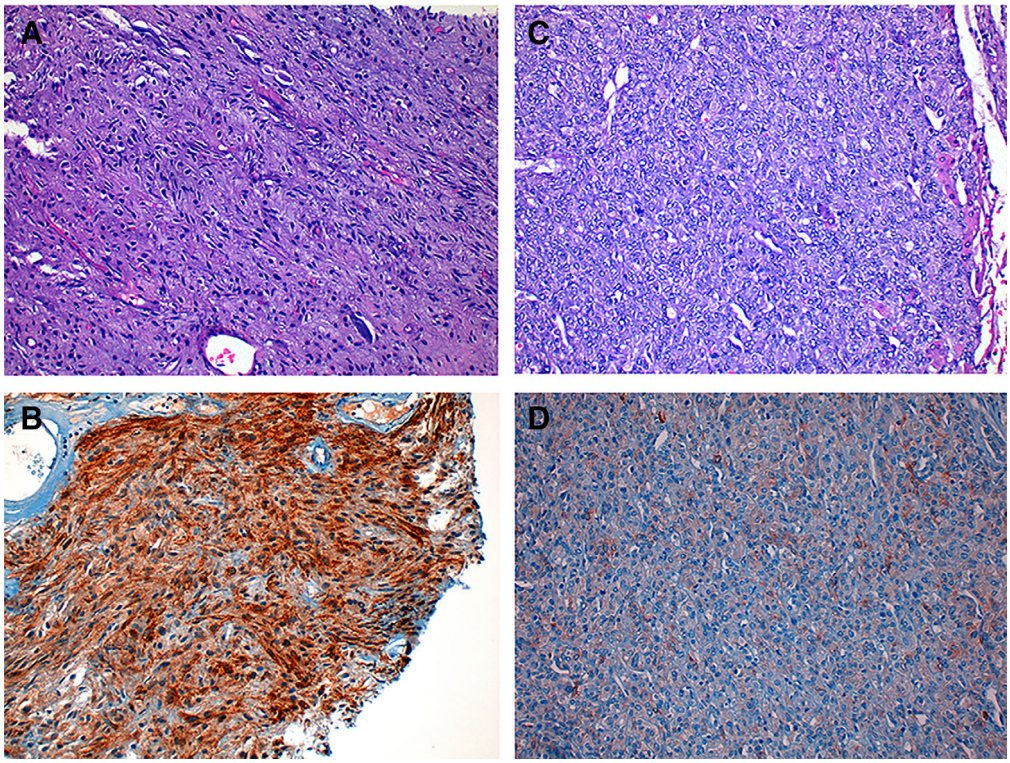

Figure 2. Case 53: Hematoxylin and eosin and c-KIT expression in baseline (before imatinib) and progressing (after imatinib) lesions. The primary tumor was predominantly fusocelullar **(A)** with an intense and diffuse c-KIT staining pattern **(B)**, whereas the lesion progression after ≥5 years was epithelioid **(C)** with weak c-KIT immunostaining **(D)**.

III trial demonstrated that PS, prior chemotherapy, tumor burden, and KIT mutation were associated with PFS in a multivariate analysis [13]. The Southwest Oncology Group trial update—although it did not examine specifically the relationship between clinicopathologic characteristics and PFS—did show the impact of age, gender, PS, tumor burden, white blood cell count, and albumin levels on OS, which can refer to some extent to long-term benefit with imatinib. Our results therefore agree with those from the two phase III trial updates [13,14] despite the so-called tumor burden category being measured differently: as the size of the largest lesion in the clinical trials, and as total number of measurable metastases in our series. Interestingly, response to imatinib has never predicted better PFS on imatinib [6,8,9]. However, in the B2222 trial update, 34% of the responding patients were progression-free after 5 years, in comparison with 22% in those achieving SD [7]. Moreover, PFS after imatinib discontinuation in the BFR14 trial was superior in patients showing CR or PR [10]. Thus, although the retrospective nature of our study hinders discrimination between CR and nonmeasurable residual disease, the accumulative evidence suggests that at least a subset of patients with GIST might obtain durable benefit if profound responses are achieved.

Overall, the aforementioned differential characteristics found in our series support that LTR behaves as a separate subgroup with less aggressive behavior and exquisite sensitivity to KIT inhibition. The biological basis is unknown, but, given the similar profile of *KIT* exon 11 mutations across both groups, it is possible that some steps of the typical cytogenetic progression from microGIST to metastatic GIST are missed during tumor evolution in LTRs [5,19]. Nonetheless, more studies are warranted to identify molecular biomarkers for LTR at baseline, as few prognostic factors at baseline have emerged from this and prior studies [7,13,14]. This is nontrivial, because a priori stratification of patients with GIST according to response could modify management and follow-up, given the striking differences in PFS and OS. In the meantime, patients with metastatic GIST with showing these favorable clinicopathologic features typical of LTRs and achieving a partial-to-complete response might be subjected to less intense monitoring, aiming to reduce patient inconvenience, exposure to radiation, and burden on the health care system.

Our study has the known intrinsic limitations of any retrospective investigation, and we subsequently included a control cohort to put our results in perspective. All patients with GIST in the control cohort had the same inclusion and exclusion criteria as LTRs, except that none of them had reached 5 years on continuous imatinib. Only 25% (n = 18) of controls were on imatinib at the cutoff, and, therefore, it is expected that a very small number of these patients will become LTR [7,13,14]. Indeed, outcomes from the control group were comparable with those reported in clinical trials [6–8]. Furthermore, and in order to measure the true magnitude of imatinib's effect, patients undergoing surgery while on imatinib were excluded from our series, as retrospective studies have consistently shown the positive impact of cytoreductive surgery on PFS and OS [20].

We also provide novel insights derived from the long-term follow-up. New adverse events emerge in up to one fourth of patients with GIST after ≥5 years on continuous imatinib therapy, although they are overall mild, manageable, and resolved after temporary interruption of imatinib. Some uncommon toxicities were found, such as renal function impairment, which has been described after several years of imatinib therapy in patients with chronic myeloid leukemia [21]. Also, the patient with bilateral osteonecrosis of femoral heads did not have known risk factors and was not on corticosteroids, and thus we consider that KIT inhibition with imatinib most likely caused this toxicity, as described with other tyrosine kinase inhibitors with activity against KIT [21,22].

Three progressive sequenced cases did not harbor KIT/PDGFRA secondary mutation, the typical mechanism of resistance to imatinib in up to 80%–90% of metastatic GIST [11,12]. Although imatinib plasma levels might have dropped over time [23], at least one patient had an uncontroversial phenotype shift at the time of progression. Further studies are needed to dimension KIT secondary mutations, but it appears that different mechanisms might emerge after years on imatinib. Finally, from our series is difficult to state that some LTRs are potentially cured. One patient relapsed after 2.3 years of imatinib discontinuation, and the remaining five patients were still on follow-up and thus likely to recur over time [10].

Conclusion

Our studies identify GIST in LTRs as a distinctive entity with less aggressive behavior and marked sensitivity to KIT inhibition. Further efforts should focus on determining the biological basis of this phenomenon and also aim to provide reliable markers for the identification of these patients upfront.

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Disclosures

César Serrano: Deciphera Pharmaceuticals, Bayer Healthcare (RF), Deciphera Pharmaceuticals (SAB), Bayer Healthcare (H); **Claudia Valverde:** Novartis, Pfizer, Eli Lilly & Co., PharmaMar (RF), Eli Lilly & Co., PharmaMar, Pfizer, Novartis (SAB), Eli Lilly & Co., Novartis, PharmaMar, Bayer (H). The other authors indicated no financial relationships.

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For Further Reading:
Robert G. Maki, Jean-Yves Blay, George D. Demetri et al. Key Issues in the Clinical Management of Gastrointestinal Stromal Tumors: An Expert Discussion. ***The Oncologist*** 2015;20:823–830.

Implications for Practice:
The treatment of gastrointestinal stromal tumor (GIST) has become sophisticated with the availability of three approved agents in many countries and 15 years of experience with primary and metastatic disease. Important lessons from tyrosine-kinase inhibitors in GIST can be gleaned from this experience and will impact implementation of similar agents for other cancers.