JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(11)1020–1027
doi:10.1093/jjco/hys138
Advance Access Publication 5 September 2012

The Lack of CD34 Expression in Gastrointestinal Stromal Tumors is Related to Cystic Degeneration Following Imatinib Use

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Received March 8, 2012; accepted August 3, 2012

Objective: We evaluated the characteristics of the gastrointestinal stromal tumors that showed discrepancies between their assessment using the Response Evaluation Criteria in Solid Tumor (RECIST) and Choi's criteria. We also investigated the clinical applicability of Choi's criteria to Korean gastrointestinal stromal tumor patients undergoing imatinib therapy.
Methods: Patients with advanced gastrointestinal stromal tumors treated with frontline imatinib were analyzed. Computed tomography images of these patients were reviewed and genotyping for the *KIT* and *PDGFRA* genes was performed. Immunohistochemical staining of c-KIT, CD34, platelet derived growth factor receptor-alpha, platelet derived growth factor receptor-beta, AKT, *P*-ERK and vascular endothelial growth factor was followed.
Results: Ninety-five patients were enrolled. When using Choi's criteria to evaluate the 61 patients who achieved at least partial response by Choi's criteria, 27 patients showed discrepancies in their response to treatment between these two sets of criteria. A lack of CD34 expression in tumors was found to be related to cystic degeneration after imatinib treatment ($P = 0.001$). Patients who showed partial response by Choi's criteria but stable disease by RECIST criteria had a similar progression-free survival to cases who showed a partial response under both systems ($P = 0.951$).
Conclusions: Gastrointestinal stromal tumors showing cystic degeneration after imatinib treatment lack CD34 expression. Choi's criteria have a clinical value in terms of the progression-free survival in Korean patients treated with imatinib.

Key words: gastrointestinal stromal tumor – imatinib – VEGF – CD34 – Choi's criteria

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common neoplasms of mesenchymal origin that arise in the gastrointestinal tract, which is highly resistant to conventional chemotherapy (1). Imatinib (Glivec®; Novartis, Basel, Switzerland) is the current treatment of choice for advanced GISTs (2), and the introduction of imatinib dramatically improves the survival outcomes for patients with metastatic GIST.

Recently, radiologic response patterns to imatinib have become an important consideration for clinicians treating GIST patients with this drug. Choi et al. (3) have shown that cystic changes, regardless of size reduction, correlate with the positron emission tomography results in patients treated

with imatinib. This finding led to the development of new response evaluation criteria for GIST patients treated with imatinib (4), and this is now reflected in the current clinical practice guidelines (5). However, there have been few studies to date on this issue and the long-term clinical implications of Choi's criteria are not yet known.

On the other hand, almost nothing is currently known about the biology of tumors that show preferential cystic changes following imatinib treatment. In fact, preferential cystic changes are related to discrepancies in the determined response of GIST patients to imatinib using Response Evaluation Criteria in Solid Tumors (RECIST) (6) and Choi's criteria. Two examples of discrepancies are (i) tumors that show initial cystic changes without a decrease in size [partial response (PR) by Choi's criteria but stable disease (SD) by RECIST], and a size reduction thereafter (i.e. they subsequently achieve PR by RECIST), and (ii) tumors showing only cystic changes without a decrease in size (PR by Choi's criteria, but SD by RECIST). Hence, pathologically, it is believed that tumors showing discrepancies between RECIST and Choi's response outcomes are undergoing preferential cystic degeneration as a result of imatinib treatment. Thus far, however, no single study has evaluated the characteristics of GISTs that undergo preferential cystic degeneration. However, considering the fact that a large proportion of GISTs show cystic or myxoid degeneration with imatinib treatment (7,8) and that nodules within a mass pattern (9), re-growth and imatinib resistance are observed in tumors showing cystic changes (10), it is worthwhile to evaluate GISTs showing preferential cystic degeneration to further understand the biology of these tumors.

We speculated that by analyzing tumor characteristics according to whether they show discrepancies in their response classification between RECIST and Choi's criteria following imatinib treatment, we would be able to discern characteristics of these lesions that could be attributed to preferential cystic change. Hence, we studied a cohort of Korean GIST patients who had undergone frontline imatinib therapy at our institution. We re-evaluated the tumor responses according to both RECIST (6) and a modified version of Choi's criteria (3), and then analyzed the biology of the tumors showing cystic changes. The tumor characteristics we evaluated included immunohistochemical (IHC) markers (c-KIT, CD34, desmin, SMA, S-100 and vimentin) used in the differential diagnosis of GIST and genotyping. We additionally performed IHC analysis of the factors involved in the imatinib treatment pathway, platelet-derived growth factor receptor-alpha (PDGFR-α), PDGFR-beta (PDGFR-β), AKT, *P*-ERK and vascular endothelial growth factor (VEGF), to determine whether their expression is related to cystic degeneration. Considering the fact that radiologic cystic change of a tumor is necrosis or hyaline degeneration pathologically, we especially focused on CD34 and VEGF among the aforementioned molecules, which are known to be differentially expressed in a tumor.

PATIENTS AND METHODS

Study Patients and Radiologic Response Evaluation

Our study cohort comprised adult patients (≥18) who received imatinib as a frontline systemic therapy for metastatic or recurrent GIST at our centers (Seoul National University Hospital and Seoul National University Bundang Hospital) between January 2003 and December 2008. We chose only those patients for whom paraffin-embedded tumor tissue prior to imatinib treatment was available for analysis. Patient demographics, primary tumor locations, progression-free survival (PFS) of imatinib and overall survival (OS) data were obtained from medical records. Imatinib had been administered orally at a dose of 400 mg/day. This dose was reduced (to 300 mg/day and then to 200 mg/day) by the treating clinicians if adverse events occurred, depending on their type and severity.

Responses were classified as a complete response, PR, SD or progressive disease according to RECIST version 1.0 (6). We also classified the responses according to a modified version of Choi's criteria (3). Radiologic evaluations were performed by a trained radiologist (S.H.K.) in a blind fashion. Patients who showed discrepancies in their response characteristics between the RECIST and Choi evaluations were subsequently analyzed.

PFS was defined as a period from the initiation of chemotherapy to the documentation of disease progression based on RECIST (6). OS was calculated from the initiation of imatinib to death from any cause. Our study protocol was reviewed and approved by the institutional review board of Seoul National University (H0908-020-289). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed.

Tissue Microarray Construction

Slides of tumor samples stained with hematoxylin and eosin were independently reviewed by two pathologists (H.E.L. and W.-H.K.) and representative areas were marked. Duplicate core tissue biopsy specimens (2 mm in diameter) were obtained from individual paraffin-embedded samples (donor blocks) and arranged in a new recipient paraffin block (tissue array block) using a trephine apparatus (SuperBioChips, Seoul, Korea). Each tissue array block contained up to 59 specimens, which allowed all 95 cases (triplet specimens of 285) to be contained in five array blocks. Serial sections from formalin-fixed paraffin blocks were used for IHC.

Genotyping

Polymerase chain reaction amplification of genomic DNA for *KIT* and *PDGFRA* was performed and the amplification was analyzed for mutations as described previously (11).

IHC Staining for c-KIT, CD34, PDGFR-α, PDGFR-β, AKT, P-ERK and VEGF

c-KIT and CD34 IHC was performed at the time of diagnosis of GIST for differential diagnosis. Hence, for c-KIT and CD34 IHC, whole block tissue but not TMA was used. For PDGFR-α, PDGFR-β, AKT, P-ERK and VEGF, IHC was performed additionally after the diagnosis for research purpose using TMA. IHC of these molecules was performed as described previously (12–15). Paraffin sections (4 μm) were evaluated according to standard protocols. Each paraffin section was dewaxed, followed by antigen retrieval. The antibodies and subsequent reaction steps used were in accordance with the manufacturer's instructions. Antigen retrieval was performed using 0.01 M (pH 6.0) buffer followed by microwaving for 15 min. Then slides were then incubated with anti-c-KIT antibody (1:200, Dako, Glostrup, Denmark), CD34 antibody (1:300, Immunotech, Brea, CA, USA), PDGFR-α antibody (1:200, Dako), PDGFR-β antibody (1:200, Dako), AKT antibody (1:100, Epitomics, Burlingame, CA, USA), *P*-ERK antibody (1:300, Santa-Cruz, Santa Cruz, CA, USA) and VEGF antibody (1:200, Santa-Cruz). Antibody binding was detected by the UltraVision LP Detection kit (Lab Vision Corporation, Fremont, CA, USA). Mayer's hematoxylin was used as the counterstain. Various normal and cancer tissue microarray blocks were included as positive and negative controls. Tumor staining was assessed by two trained pathologists (H.E.L. and W.-H.K.) in a blind fashion. The staining intensity of PDGFR-α, PDGFR-β, AKT, *P*-ERK and VEGF was graded on a scale of 0–2 using adjacent non-malignant cells as a reference. The average expression intensity of these molecules in triplet tissue blocks was calculated and used as a representative measure of the expression intensity. The median expression intensity was used as a dichotomizing cut-off value for each molecule.

Statistical Analysis

The variables analyzed in this study included age, gender, location of the primary tumor, site of metastasis, prior treatment before imatinib, genotyping results, IHC results, the radiologic response patterns to imatinib, PFS and OS. Statistical analysis of 2×2 contingency tables of categorical variables were performed using Pearson's χ^2 test or Fisher's exact test, as appropriate. The median durations of PFS and OS were calculated using the Kaplan–Meier method and comparisons between groups were made using log-rank tests. The impact of continuous numeric variables on the clinical outcomes was calculated using logistic regression and a Cox regression model. Multivariate analyses were performed using a Cox regression model for PFS and OS. Factors with P values of <0.1 by univariate analysis were examined using multivariate regression analysis. All statistical tests were two-sided, with statistical significance defined as $P < 0.05$. All analysis was performed using Statistical Package for the Social Sciences for Windows Version 12.0 (IBM, Chicago, IL, USA).

RESULTS

Patient and Tumor Characteristics

A total of 95 patients were enrolled in this study with a median age of 59 years (range 24–86 years) and a male-to-female ratio of 55:40. For patients who had recurrent disease, the median disease-free survival was 20.4 months (range 0.57–236.3 months). Six patients received adjuvant cytotoxic chemotherapy before relapse. The positive rate for c-KIT was 96.8%. These basic patient and tumor characteristics are summarized in Table 1.

For IHC results, CD34 expression was evaluable in 90 patients and the positive rate was 80.0%. The expression of PDGFR-α, PDGFR-β, AKT, *P*-ERK and VEGF was assayed in 86, 90, 90, 81 and 91 patients, respectively. The positive expression rate of PDGFR-α, PDGFR-β, AKT, *P*-ERK and VEGF was 30.2, 37.8, 50.0, 21.0 and 45.1%, respectively. Representative examples of the corresponding IHC results are shown in Fig. 1 and Supplementary data, Fig. S1. Genotyping results were available for 83 patients. For 12 cases, these data were not available due to insufficient amounts of DNA. Mutations in *KIT* exon 11 were found in 58 patients (61.1%), *KIT* exon 9 in 7 patients (7.4%), *PDGFRA* exon 12 in 1 patient (1.1%) and *PDGFRA* exon 18 in 2 patients (2.1%). Fifteen patients showed no mutation in either *KIT* or *PDGFRA* and were thus classified as wild type. Of the three patients lacking c-KIT expression, two harbored a *PDGFRA* mutation and one showed a *KIT* exon 11 mutation.

For imatinib treatment, among the 95 patients in our cohort who received imatinib, 76 did not experience a greater than Grade 2 toxicity, thus allowing a 400 mg/day dosage to be maintained. A dose reduction to 300 mg/day was necessary for 15 patients and to 200 mg/day was required for 4 patients. Among the four cases who received a 200 mg/day administration of imatinib, two patients experienced a Grade 4 neutropenia and two a Grade 4 thrombocytopenia while receiving the 300 mg/day dose.

Response to Imatinib Treatment

In terms of the response to imatinib, 71 patients had measurable disease and hence could be assessed for their response to treatment. The overall response rate was 70.4% and the disease control rate was 93% by RECIST (Table 2). A lack of c-KIT expression was found to be associated with a poor response to imatinib ($P = 0.023$).

During the median follow-up of 53.1 months (range 2.7–104.0 months), 42 patients showed progression on imatinib with a median of 48.6 months. The expression of c-KIT was a good predictive marker of a long PFS following imatinib treatment (median PFS 45.4 vs. 3.0 months, $P < 0.001$).

Table 1. Demographics and pathologic characteristics of 95 Korean gastrointestinal stromal tumor (GIST) patients who received imatinib for advanced or recurrent disease

	Number of patients (%)
Age [median (range)]	59 (24–86)
Gender	
Male	55 (57.9)
Female	40 (42.1)
Primary location	
Stomach	37 (38.9)
Small bowel	38 (40.0)
Rectum	11 (11.6)
Omentum/mesentery	8 (8.4)
Esophagus	1 (1.1)
Disease status	
Initially metastatic	52 (54.7)
Recurrent	43 (45.3)
Liver metastasis[a]	
Yes	60 (63.2)
No	35 (36.8)
c-KIT expression	
Yes	92 (96.8)
No	3 (3.2)
CD34 expression	
Yes	76 (80.0)
No	14 (14.7)
Desmin expression	
Yes	7 (7.4)
No	68 (71.6)
SMA expression	
Yes	22 (23.2)
No	58 (61.1)
S-100 expression	
Yes	18 (18.9)
No	67 (70.5)

[a]At the time of the first imatinib administration.

When the genotype was considered, patients with *KIT* exon 11 mutations had a longer PFS than those without this mutation (median PFS 89.1 vs. 34.3 months, $P = 0.015$). When *PDGFRA* mutants were compared with *KIT* exon 11 mutants, they had a significantly shorter PFS than the *KIT* exon 11 mutants (median PFS 17.2 vs. 89.1 months, $P = 0.045$).

During the same follow-up period, however, 32 patients died and the estimated median OS was calculated to be 71.5 months. We found that age had a marginally negative prognostic impact in terms of OS (hazard ratio 1.032, $P = 0.052$). The expression of c-KIT was shown to be a favorable prognostic factor in terms of OS (median OS 71.5 vs. 4.4 months, $P < 0.001$). The genotype was not found to be a prognostic factor for OS.

Response Evaluations Using Choi's Criteria

When responses were evaluated using Choi's criteria, the overall response rate and disease control rate assessed by Choi's criteria were 85.9 and 93%, respectively (Table 2). When discrepancies between the findings using RECIST and Choi's criteria were considered, 27 patients (44.3%) showed differing response outcomes among 61 subjects in our cohort who achieved at least PR by Choi's criteria. Eleven patients showed an initial cystic change without a decrease in size (PR by Choi's criteria but SD by RECIST), but size reduction thereafter (i.e. subsequently achieved PR by RECIST): Early response by Choi's criteria. The other 16 patients showed only cystic changes without a decrease in tumor size (PR by Choi's criteria but SD by RECIST criteria): Better response by Choi's criteria. Considering the fact that the original Choi's criteria were devised to find patients who would earn a long-term benefit from imatinib without an early response to imatinib by RECIST, we not only deemed the 'Better response by Choi's' group but also deemed the 'Early response by Choi's' group as patients who show discrepancies between RECIST and Choi's criteria. Representative examples of the GISTs that showed response discrepancies between RECIST and Choi's criteria are depicted in Fig. 2.

Characteristics of GISTs Showing Response Discrepancies Between RECIST and Choi's Criteria Evaluations

We evaluated the characteristics of the GISTs in patients who had measurable disease and had achieved at least PR following imatinib treatment when evaluated using Choi's criteria. A total of 61 patients fell into this category. As mentioned above, 27 of these 66 patients (44.3%) showed response discrepancies when evaluated using RECIST and Choi's criteria.

GISTs which showed discrepancies between their RECIST and Choi's criteria response evaluations were found to express CD34 less frequently than patients who showed no discrepancies ($P = 0.001$; Table 3). Characteristics of seven patients who lacked CD34 expression are shown in Table 4. The genotype and other routine IHC markers used for differential diagnosis (c-KIT, Desmin, SMA and S-100) were found not to be associated with the response discrepancies. In addition, none of the markers PDGFR-α, PDGFR-β, AKT, *P*-ERK or VEGF were found to be related to cystic degeneration. These results are summarized in Table 3.

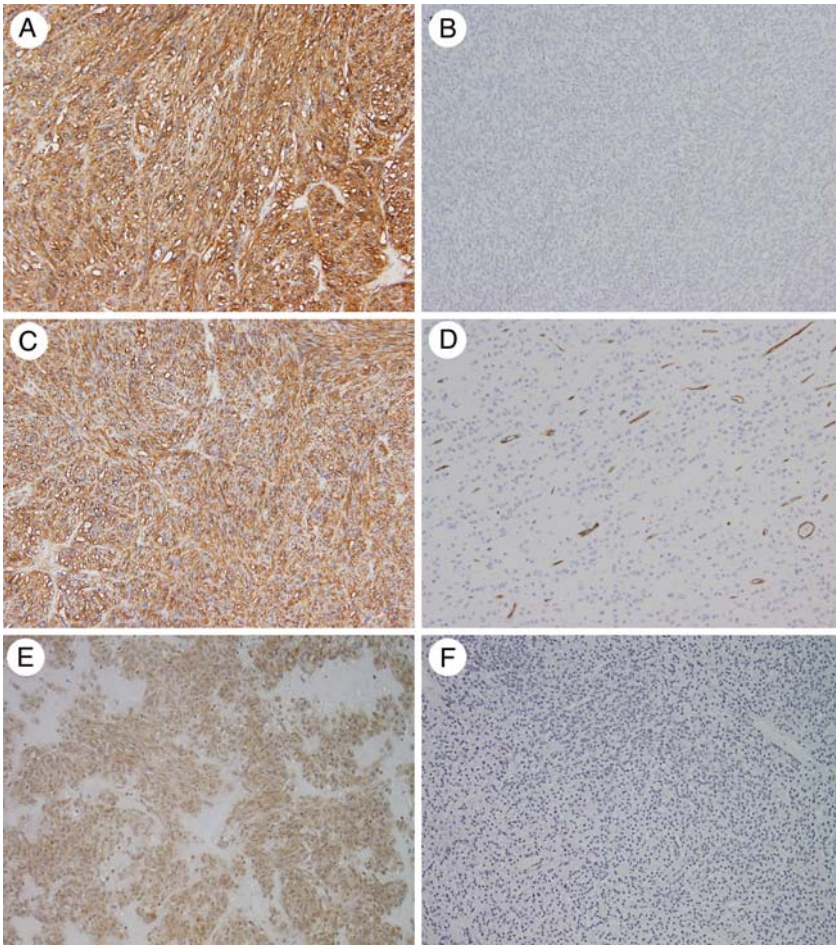

Figure 1. Representative examples of c-KIT, CD34 and vascular endothelial growth factor (VEGF) immunostaining. Figures (A) through (F) show tumors with the positive and negative expression of c-KIT, CD34 and VEGF, respectively.

Table 2. Response evaluation by RECIST and Choi's criteria

	CR (*n*, %)	PR (*n*, %)	SD (*n*, %)	PD (*n*, %)
Imatinib response[a]				
RECIST	5 (7.0)	45 (63.4)	16 (22.5)	5 (7.0)
Choi's criteria	5 (7.0)	56 (78.9)	5 (7.0)	5 (7.0)

[a]Seventy-one of 95 patients had measurable disease.

Long-term Clinical Impact of Choi's Criteria

Patients who showed PR by Choi's criteria but SD by RECIST (Better response by Choi's criteria) had a similar PFS to the patients who showed PR using both sets of criteria (median PFS 49.0 vs. 37.0 months, $P = 0.951$; Fig. 3). In addition, patients who showed early PR by Choi's criteria had a similar PFS to patients who did not show early PR by Choi's criteria (median PFS 39.0 vs. 37.0 months, $P = 0.894$; Fig. 3). The radiologic response pattern did not affect OS.

DISCUSSION

In our present study, we analyzed the radiologic response patterns of GISTs to imatinib treatment and reveal novel findings. First of all, our data show that patients who showed PR by Choi's criteria but SD by RECIST (Better response by Choi's criteria) had a similar PFS to patients who showed PR by RECIST criteria. This provides additional evidence that Choi's criteria have a long-term clinical value in assessing the treatment of GIST patients with imatinib (4). In addition, considering our observations of the distinct clinical features of Korean GIST patients treated with imatinib, including a relatively long PFS and good response rate, our present data also confirm that Choi's criteria are clinically applicable to Asian GIST cohorts undergoing this therapy. However, it should be noted that our results do not assert that RECIST criteria are not applicable in Asian patients or that they are inferior to Choi's criteria in this regard. The design of our study does not allow a direct comparison of the two sets of criteria. Moreover, there is evidence that both RECIST (11) and Choi's criteria (3) are clinically valuable in assessing the response of GISTs to treatment. The relative

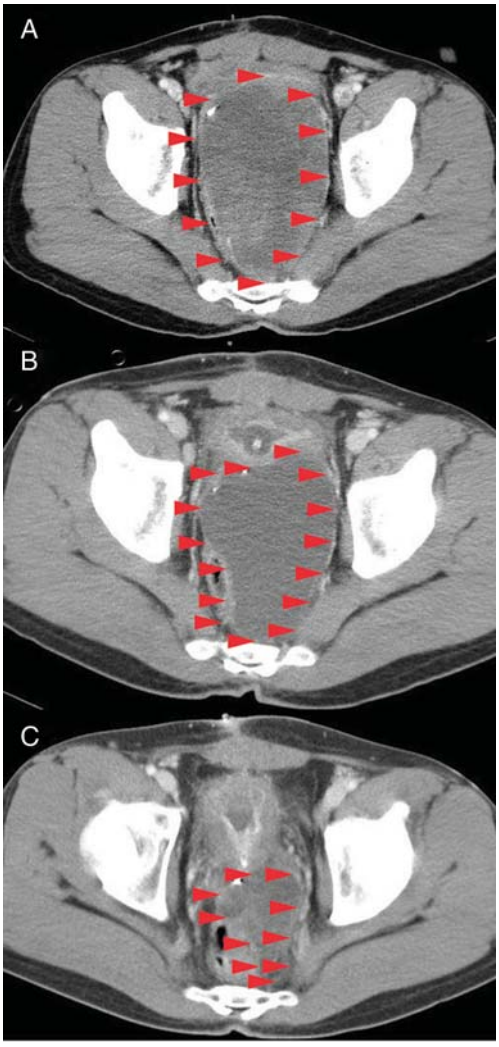

Figure 2. Representative computed tomography scans of gastrointestinal stromal tumor (GIST) patients showing response discrepancies between RECIST and Choi's criteria. The tumor of a 41-year-old male (A) with an initial cystic degeneration without significant size change is shown (B). At 3 months later, this same tumor had reduced to 39.4% of its original size (C).

Table 3. Characteristics of GISTs showing and not showing response discrepancies when evaluated using RECIST and Choi's criteria[a]

	Discrepancies (+) ($n = 27$)	Discrepancies (−) ($n = 34$)	*P* value
c-KIT expression			
Positive	26	34	0.443
Negative	1	0	
CD34 expression			
Positive	17	33	0.001
Negative	7	0	
Genotype			
KIT exon 11	16	21	0.888
KIT exon 9	4	3	
PDGFRA	1	2	
Wild type	3	4	
PDGFR[b] expression			
Positive	12	11	0.472
Negative	14	19	
P-ERK expression			
Positive	2	7	0.160
Negative	22	22	
AKT expression			
Positive	10	15	0.452
Negative	16	16	
VEGF expression			
Positive	12	15	0.956
Negative	14	17	

PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor.
[a]Evaluated in 61 patients who achieved at least PR by Choi's criteria.
[b]Expression of either PDGFR-α or PDGFR-β.

strengths of the two sets of criteria will need to be addressed in future studies with a proper design.

The highlight of our study is that we explored for the first time the biologic properties of GISTs showing response discrepancies when assessed by RECIST and Choi's criteria. As stated earlier, for this issue, we particularly focused on two molecules CD34 and VEGF, which are known to be related to the tumor vasculature (16–18). It is from the well-known fact that cystic change of a tumor in radiologic assessment is closely related to the myxoid degeneration, hyalinization or necrosis of the tumor pathologically. And as expected, whereas the genotypes of the tumors in our study cohort did not correlate with their radiologic response patterns, the lack of CD34 expression was found to be related to a dominant cystic change in these lesions after imatinib treatment. CD34 is a stem cell marker that represents high proliferation of tumor cells. In this sense, too, it is theoretically explained that tumors lacking CD34 expression exhibit slow tumor shrinkage with cystic degeneration following imatinib treatment. We postulate that because CD34 is a stem cell marker, there is a chance that stem cell characteristics represented by CD34 might play a key role in this phenomenon.

On the other hand, we found that VEGF expression did not correlate with cystic degeneration in GISTs. VEGF expression has been shown previously to be related to aggressive tumor behavior in these tumors (19,20); however, it was not related to necrosis following imatinib treatment in our study. Although we showed a phenotypic correlation between CD34 and cystic change of GISTs following imatinib treatment, the precise roles of CD34 and VEGF in GISTs are not yet well understood and further studies will be required to elucidate functions of these molecules.

Table 4. Characteristics of seven patients[a] whose tumor lacked CD34 expression

ID	Age	Gender	VEGF expression	Mutation status	Best response by RECIST	Best response by Choi's	PFS	OS
1	68.9	M	0	Exon11	PR	PR	39.03	43.03
2	61.4	F	0	Exon9	PR	PR	22.73	30.23+
3	58.4	F	1	PDGFRA	SD	PR	17.2	49.57
4	75.2	F	1	Exon11	PR	PR	32.23	47.5
5	77.8	F	1	Unknown	SD	PR	4.67+	6.27+
6	38.3	M	0	Exon11	SD	PR	32.13+	75.33+
7	36.5	F	0	No mutations	PR	PR	40.93+	43.9+

[a]All seven patients showed discrepancies between RECIST and Choi's criteria.

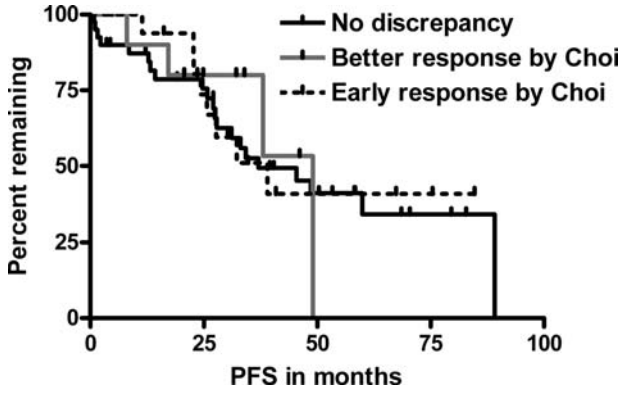

Figure 3. The progression-free survival (PFS) associated with imatinib according to response discrepancies when evaluated by RECIST and Choi's criteria. Discrepancies in the response outcomes determined by RECIST and Choi's criteria do not affect the PFS of GIST patients treated with imatinib. Tumors showing preferential cystic degeneration had a similar clinical value in terms of PFS with lesions showing partial response by RECIST and that did not show preferential cystic degeneration.

In our present study cohort, Korean GIST patients treated with frontline imatinib had a relatively long PFS of 48.6 months and a high disease control rate of 93%. This is similar to the results of a previous prospective phase II study from Korea (21). On the other hand, a favorable predictive impact of c-KIT expression and *KIT* exon 11 mutations, and an unfavorable predictive impact of *PDGFRA* mutation, was evident from our current patients, consistent with previous reports of GIST cohorts from western countries (22). The reasons why imatinib shows a relatively higher efficacy in Asian patients is not yet fully understood. However, given the previously determined correlation between the imatinib plasma trough levels and the clinical outcome (23), we believe that pharmacokinetic approaches may help to explain these phenomena in the future.

In conclusion, Choi's criteria have clinical value in terms of PFS in Asian GIST patients treated with imatinib. Interestingly, tumors showing cystic degeneration after imatinib treatment lack CD34 expression. However, VEGF expression does not correlate with cystic degeneration following imatinib therapy. It is noteworthy also that our present study is an anecdotal report that explores the biological properties of GISTs showing cystic changes following targeted therapy. Because not much is known about the clinical importance of cystic degeneration in these tumors, our findings will not yet directly benefit the current treatment practices for these lesions. However, we believe that our novel results will have long-term benefits for our understanding of this disease.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Funding

This study was supported in part by a research grant from the Cancer Research Institute, Seoul National University (2009) to S.A.I. (CRI-09-6).

Conflict of interest statement

None declared.

References

1. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. *Lancet* 2007;369:1731–41.
2. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008;19(Suppl 2):ii35–8.
3. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 2007;25:1753–9.
4. Benjamin RS, Choi H, Macapinlac HA, et al. We should desist using RECIST, at least in GIST. *J Clin Oncol* 2007;25:1760–4.

5. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)—update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw* 2007;5(Suppl 2):S1–29; quiz S30.
6. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
7. Bechtold RE, Chen MY, Stanton CA, Savage PD, Levine EA. Cystic changes in hepatic and peritoneal metastases from gastrointestinal stromal tumors treated with Gleevec. *Abdom Imaging* 2003;28:808–14.
8. Linton KM, Taylor MB, Radford JA. Response evaluation in gastrointestinal stromal tumours treated with imatinib: misdiagnosis of disease progression on CT due to cystic change in liver metastases. *Br J Radiol* 2006;79:e40–4.
9. Shankar S, vanSonnenberg E, Desai J, Dipiro PJ, Van Den Abbeele A, Demetri GD. Gastrointestinal stromal tumor: new nodule-within-a-mass pattern of recurrence after partial response to imatinib mesylate. *Radiology* 2005;235:892–8.
10. Desai J, Shankar S, Heinrich MC, et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. *Clin Cancer Res* 2007;13(18 Pt 1):5398–405.
11. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 2003;21:4342–9.
12. Kubo T, Piperdi S, Rosenblum J, et al. Platelet-derived growth factor receptor as a prognostic marker and a therapeutic target for imatinib mesylate therapy in osteosarcoma. *Cancer* 2008;112:2119–29.
13. Bauer S, Duensing A, Demetri GD, Fletcher JA. KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway. *Oncogene* 2007;26:7560–8.
14. Chadha KS, Khoury T, Yu J, et al. Activated Akt and Erk expression and survival after surgery in pancreatic carcinoma. *Ann Surg Oncol* 2006;13:933–9.
15. McAuliffe JC, Lazar AJ, Yang D, et al. Association of intratumoral vascular endothelial growth factor expression and clinical outcome for patients with gastrointestinal stromal tumors treated with imatinib mesylate. *Clin Cancer Res* 2007;13(22 Pt 1):6727–34.
16. Fina L, Molgaard HV, Robertson D, et al. Expression of the CD34 gene in vascular endothelial cells. *Blood* 1990;75:2417–26.
17. Stella CC, Cazzola M, De Fabritiis P, et al. CD34-positive cells: biology and clinical relevance. *Haematologica* 1995;80:367–87.
18. Ganjoo K, Jacobs C. Antiangiogenesis agents in the treatment of soft tissue sarcomas. *Cancer* 2010;116:1177–83.
19. Sherbenou DW, Wong MJ, Humayun A, et al. Mutations of the BCR-ABL-kinase domain occur in a minority of patients with stable complete cytogenetic response to imatinib. *Leukemia* 2007;21:489–93.
20. Yeh CN, Chen TW, Lee HL, et al. Kinase mutations and imatinib mesylate response for 64 Taiwanese with advanced GIST: preliminary experience from Chang Gung Memorial Hospital. *Ann Surg Oncol* 2007;14:1123–8.
21. Ryu MH, Kang WK, Bang YJ, et al. A prospective, multicenter, phase 2 study of imatinib mesylate in Korean patients with metastatic or unresectable gastrointestinal stromal tumor. *Oncology* 2009;76:326–32.
22. Judson IR. Prognosis, imatinib dose, and benefit of sunitinib in GIST: knowing the genotype. *J Clin Oncol* 2008;26:5322–5.
23. Widmer N, Decosterd LA, Leyvraz S, et al. Relationship of imatinib-free plasma levels and target genotype with efficacy and tolerability. *Br J Cancer* 2008;98:1633–40.