Targeted therapy, molecular imaging and biomarkers in cancer treatment

den Hollander, Martha Willemine

Chapter 3

^{18}F-FDG-PET response no early predictive marker for primary imatinib resistance in patients with gastrointestinal stromal tumors

S.F. Oosting [1], M.W. den Hollander [1], B. Rikhof [1], D.B. Rouw [2], J.R. de Jong [3], P.L. Jager [4], A.H. Brouwers [3], A.J.H. Suurmeijer [5], W.J. Sluiter [6], W.T.A. van der Graaf [7], E.G.E. de Vries [1], J.A. Gietema [1], A.K.L. Reyners [1]

Departments of [1]Medical Oncology, [2]Radiology, [3]Nuclear Medicine and Molecular Imaging, [5]Pathology, [6]Endocrinology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands. [4]Department of Nuclear Medicine, Isala Clinics, Zwolle, The Netherlands. [7]Department of Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

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ABSTRACT

Background: Approximately 15% of gastrointestinal stromal tumor (GIST) patients show primary resistance to imatinib, defined as progressive disease on CT after 8 weeks. We investigated whether early change in tumor ^{18}F-fluorodeoxyglucose uptake on positron emission tomography (FDG-PET) predicts primary imatinib resistance.

Methods: 36 metastatic or locally advanced GIST patients underwent FDG-PET scans before and 1 week after start of imatinib. Relationship between FDG-PET response (EORTC criteria) and CT response after 2 months of treatment (RECIST 1.0 and Choi criteria) was investigated. FDG uptake was measured as Standardized Uptake Value (SUV).

Results: Of the 30 patients evaluable with FDG-PET, 26 experienced a response and 4 had stable disease. Mean tumor SUV_{max} decreased from 7.4 (SD 3.8, range 2.2-18.4) to 3.0 (SD 2.1, range 0.1-11.8) after 1 week imatinib ($P < 0.001$). FDG-PET response had a high positive predictive value for clinical benefit (response or stable disease) according to RECIST 1.0: 92% (95% CI 75-99%) and Choi: 95% (95% CI 76-100%). The false negative rate was respectively 11% (95% CI 2-30%) and 9% (95% CI 1-30%).

Conclusion: While FDG-PET response has a high positive predictive value for clinical benefit of imatinib in GIST patients, it does not predict primary resistance.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors that arise in the gastrointestinal tract. They are characterized by expression of CD117; the KIT receptor. Approximately 80% of all GISTs have a gain of function mutation in *KIT* resulting in constitutive activation and continuous downstream signaling. Furthermore, 5-10% of GISTs have an activating mutation in the gene encoding platelet derived growth factor receptor α (*PDGFRA*). Imatinib is an oral tyrosine kinase inhibitor that inhibits signaling of both KIT and PDGFRα. The majority of patients with unresectable or metastatic GIST benefits from treatment with imatinib [1]. However, ± 15% of GIST patients have primary imatinib resistant disease, i.e. progressive disease within 3 months after start of treatment [2]. Earlier or upfront identification of primary resistance would spare these patients the side effects of ineffective therapy and allow an earlier switch to alternative treatment. To date, no predictive biomarkers to guide treatment decisions are available. However, it is well appreciated that imatinib can induce a rapid and dramatic decrease in glucose uptake in GIST [3-6].

The objective of this study was to investigate whether metabolic response early after initiation of treatment can be used to predict primary resistance to imatinib in patients with locally advanced or metastatic GIST. In addition, we studied whether the metabolic response correlated with progression free survival (PFS) or specific receptor tyrosine kinase gene mutations.

MATERIALS AND METHODS

Patients and study design

This is a retrospective analysis of consecutive patients with newly diagnosed locally advanced, metastatic or recurrent GIST, who started treatment with imatinib between February 2001 and October 2007 at the University Medical Centre Groningen (UMCG). Imatinib was administered orally at 400 to 800 mg per day. Fourteen patients were part of an earlier study [4].

FDG-PET

FDG-PET scans at baseline and after 1 week imatinib treatment were standard care from February 2001 for patients with advanced GIST in the UMCG. As of October 2007, a different PET scan protocol was used. Therefore, this analysis is restricted to GIST patients who underwent PET scans before October 2007. PET scans were performed on a Siemens ECAT EXACT HR+ scanner in 2D mode. Patients fasted for 6 hours. Ninety min after injection of 5 MBq/kg ^{18}F-FDG, a whole body scan was performed (7-8 bed positions from femur to crown, 8 min per bed position of which 3 min transmission time). The iterative reconstruction algorithm AW-OSEM 2D was used with 2 iterations, 8 subsets and a Gaussian filter of 10 mm.

For each patient, a maximum of 5 target lesions was used for tumor evaluation. Target lesions were defined as the 5 most intense FDG accumulating tumor lesions. The FDG uptake was measured by calculating the Standardized Uptake Value (SUV) as described earlier in regions of interest (ROI) placed over tumor lesions, with Siemens Leonardo software [7]. The maximum SUV (SUV_{max}) and the uptake in the 3-dimensional isocontour at 70% and at 40% of the maximum

pixel value (SUV70 and SUV40) for each target lesion was measured. For all target lesions in a patient the mean SUV_{max}, the mean SUV70 and the mean SUV40 was calculated for both scans. For classification of metabolic tumor response, the EORTC criteria for FDG-PET imaging were used [7]. Also the previously reported thresholds for the single lesion with the most intense uptake at baseline (25% reduction, 40% reduction, <2.5 and <3.4 for SUV_{max} on the second scan) were tested [8] and the definition of metabolic response used by Choi et al (decrease of mean SUV_{max} with ≥70% to less than 2.5) [9].

CT scan

CT scans were performed at baseline, after 8 weeks and every 3 months thereafter. For response classification, Response Evaluation Criteria for Solid Tumors (RECIST) version 1.0 was used as well as the criteria described by Choi et al [9,10].

Mutation analysis

Mutation analysis of *KIT* exons 9, 11, 13 and 17 and *PDGFRA* exons 12, 14 and 18 was performed as described previously [11].

Outcome parameters

Primary resistance is defined as progressive disease after 8 weeks of treatment according to RECIST1.0 or the Choi criteria. Positive predictive value, negative predictive value and false negative rate of FDG-PET for primary resistance were calculated with 95% confidence intervals (CI).

Progression free survival (PFS) was defined as the time from imatinib initiation until disease progression or death, whichever occurred first. For PFS analysis, the occurrence of a new lesion, or an increase in size of pre-existing lesions (as defined by RECIST 1.0), or development of an intra-tumoral nodule and/or an increase in 'solid' tissue, in the background of a hypodense lesion were considered progressive disease according to the ESMO guidelines for GIST [12,13].

Statistics

For comparison of the mean SUV at the first and second FDG-PET scan, the Wilcoxon signed rank test was used. PFS was estimated with the Kaplan-Meier method. Patients were censored at the date of surgery for complete surgical resection and at the date of last follow up for patients alive and progression free at the time of analysis.

RESULTS

Patients

Thirty six patients with a mean age of 62 years (range 23 - 81) were included. Nine patients had locally advanced disease and 27 patients had metastatic or recurrent disease. For characteristics see Table 1. Two patients started with imatinib 400 mg 2 times daily, the others with 400 mg once daily. The median follow-up time was 35 months (range 4 - 87+). In patients who received imatinib with a non-curative intent, median PFS was 23 months (range 2 - 83+ months) and in this subgroup median overall survival was 32 months (range 4 - 87+ months). Twelve patients received subsequent systemic treatment upon disease progression.

Table 1. Patient characteristics.

Characteristics	Total (N = 36)
Age (years)	
Median	62
Range	23-81
Sex, N (%)	
Male	22 (61)
Female	14 (39)
Treatment setting, N (%)	
Neo-adjuvant	7 (19)
Palliative	29 (81)
Primary site, N (%)	
Stomach	13 (36)
Small bowel	14 (39)
Colon	3 (8)
Other	6 (17)
Metastatic sites, N (%)	
Liver	11 (31)
Peritoneal cavity	8 (22)
Liver and peritoneal cavity	6 (17)
Other	2 (6)
Mutation type, N (%)	
KIT exon 11	15 (42)
KIT exon 9	5 (14)
PDGFRA exon 18	3 (8)
Wild typea	2 (6)
Unknown	11 (31)

N: number of patients

a No KIT or PDGFRA mutation

FDG-PET assessment

The baseline FDG-PET scan was performed at a median of 2 days (range 1 - 46) before start of treatment. Four patients had no FDG-avid lesions and therefore did not undergo a second FDG-PET scan. These four patients had normal blood glucose levels and were not on glucose lowering medication. The repeat scan was performed at median 8 days (range, 6-10) after start of imatinib. In two patients, a different FDG-PET imaging protocol was used for the baseline and repeat scan; these patients were therefore excluded from the analysis, resulting in 60 FDG-PET scans of 30 patients available for quantification of metabolic response. Tumor FDG-uptake decreased from baseline with a mean SUV_{max} of 7.4 (SD 3.8, range 2.2 - 18.4) to a mean SUV_{max} of 3.0 (SD 2.1, range 0.1 - 11.8, $P < 0.001$) after 1 week imatinib (Fig. 1).

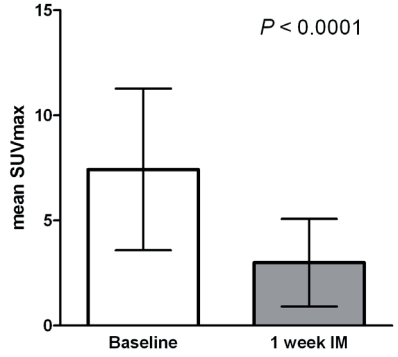
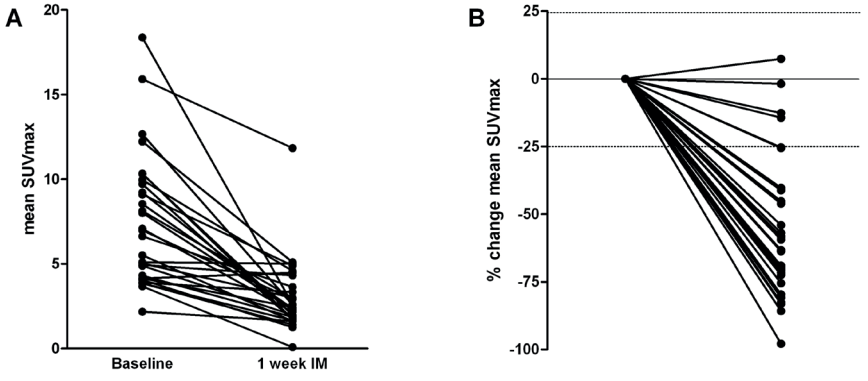


Figure 1. (left) Tumor FDG uptake (in mean SUV_{max} with standard deviation) in 30 GIST patients before start and after 1 week imatinib (IM) treatment.

Figure 2. (below) A. Absolute and B. relative changes in tumor FDG uptake (in mean SUV_{max}) in individual patients (N = 30) in up to 5 tumor lesions between baseline PET scan and PET scan after 1 week imatinib (IM) treatment. Grey dotted lines shows thresholds for response (-25%) and progressive disease (+25%) according to EORTC criteria.



Relative changes in mean SUV_{max} for individual patients ranged from +7.3% to -97.8% (Fig. 2B). Based on change of mean SUV_{max}, 26 patients experienced a metabolic response according to EORTC criteria and four patients had metabolic stable disease (hereafter called non-responders). None of the patients had metabolic progressive disease. Analysis of mean SUV40 and mean SUV70 revealed a similar pattern with 26 responders and four non-responders, although according to mean SUV70, one non-responder had metabolic progressive disease.

Predictive value of metabolic response

One out of 30 patients had non-measurable disease on CT, therefore data of 29 patients were available for response classification according to RECIST. Two patients had progressive disease, i.e. primary imatinib resistance. In six patients Hounsfield Units could not be measured, therefore evaluation according to the Choi criteria could be applied in 23 patients (Table 2). Positive predictive value of a metabolic response (estimated with mean SUV_{max}) for clinical benefit from imatinib is 92% (95% CI 75 - 99%) for RECIST and 95% (95% CI 76 - 100%) for the Choi criteria. As none of the metabolic non-responders in our cohort had primary imatinib resistant disease, a negative predictive value could not be calculated. The false negative rate of FDG-PET for prediction of clinical benefit from imatinib was 11% (95% CI 2-30%) for RECIST and 9% (95% CI

1–30%) for the Choi criteria. Of the four patients with a negative baseline FDG-PET scan, three had clinical benefit (two partial responses and one stable disease) and one had progressive disease according to RECIST. Based on the Choi criteria two out of three derived benefit from imatinib (both partial responses) whereas the third patient had primary resistant disease.

Table 2. FDG PET versus CT response.

	CT scan			
	RECIST (N = 29)		Choi (N = 23)	
	CR/PR/SD[a]	PD	CR/PR/SD[b]	PD
FDG-PET scan				
Response[c]	24	2	20	1
No response	3	0	2	0

FDG-PET response after 1 week and CT response after 8 weeks of imatinib treatment.

N = number of patients, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

[a] CR (N = 1), PR (N = 9), SD (N = 17)

[b] CR (N = 1), PR (N = 16), SD (N = 5)

[c] decrease in mean SUVmax ≥ 25% and no new lesions and no visible increase in extent of tumor FDG-uptake >20% in the longest dimension

For mean SUV70 identical predictive values for primary imatinib resistant disease as for mean SUV_{max} were obtained and mean SUV40 performed worse. There was no difference in PFS between metabolic responders, non-responders and patients with non FDG-avid lesions when using mean SUV_{max} according to the EORTC criteria (Fig. 3). This was also the case for mean SUV70, mean SUV40, for the definition of response used by Choi et al and for SUV_{max} of the single lesion with the most intensive uptake at baseline according to the thresholds described by Holdsworth et al [8,9].

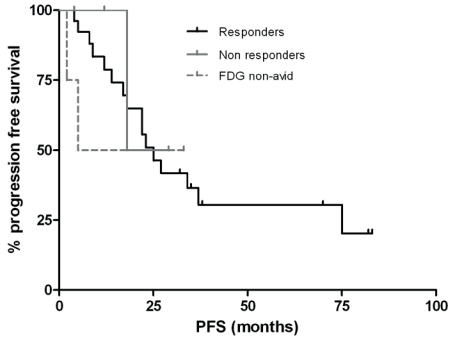


Figure 3. PFS in patients with a metabolic tumor response (***N*** = 26, black line), patients without metabolic response (***N*** = 4, grey solid line) and in patients with non FDG-avid tumor lesions (***N*** = 4, grey dashed line). No difference in PFS was found.

Mutation analysis and metabolic response

In 25 of 36 patients, sufficient tumor tissue was available for mutation analysis. A *KIT* exon 11 mutation was present in 15 cases (60%), a *KIT* exon 9 mutation in five (20%), a *PDGFRA* exon 18 mutation in three (12%), and no mutation was found in either *KIT* or *PDGFRA* in two patients (8%).

One patient with a *KIT* exon 9 mutation and two patients with a *PDGFRA* mutation showed no FDG uptake in tumor lesions at baseline. One patient with a *KIT* exon 11 and one patient with a *KIT* exon 9 mutation were not evaluable for metabolic response. Metabolic response for 20 patients according to mutation is shown in Fig. 4.

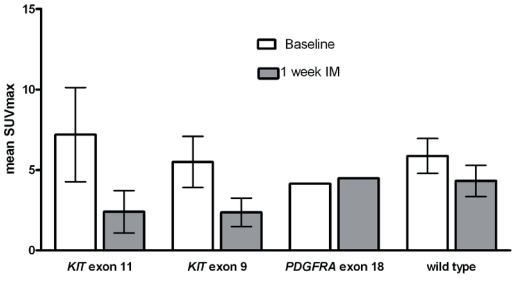


Figure 4. Change in tumor FDG uptake (mean SUV_{max} with standard deviation) after 1 week imatinib treatment according to mutation type: *KIT* exon 11 (*N* = 14), *KIT* exon 9 (*N* = 3), *PDGFRA* (*N* = 1) and in wild type tumors (*N* = 2). IM = imatinib.

DISCUSSION

The results of the current study show that early FDG-PET response cannot be used to identify primary imatinib resistant disease in patients with GIST. Absence of an early metabolic response does not indicate that patients do not benefit from imatinib.

Furthermore, patients with primary resistant disease can have a metabolic response. Although we found high positive predictive values of metabolic response for clinical benefit from imatinib (92% for RECIST and 95% for the Choi criteria) the upfront chance of response or stable disease is 85%, which falls within the 95% CI of the positive predictive value. Therefore, little if any predictive information on treatment outcome is added by early assessing metabolic response.

Stroobants et al. performed FDG-PET scans at baseline and after 1 week of imatinib treatment in 17 GIST patients [6]. From their study a positive predictive value of 92%, a negative predictive value of 75% and a false negative rate of 8% for patients who derive clinical benefit from imatinib (response plus stable disease as best response according to RECIST) can be calculated, which is comparable with our results. Recently FDG-PET results of a study on neoadjuvant imatinib treatment in operable GIST patients were reported [14]. Looking at metabolic responders versus non-responders after 1 week of treatment, a positive predictive value of 100%, a negative predictive value of 14%, and a false negative rate of 16% can be calculated for clinical benefit from imatinib, again in line with our findings. A possible explanation for incidental incongruence between antitumor activity and glucose uptake is given by Tarn et al [15]. They demonstrated in

Table 3. Summary of studies investigating the role of FDG PET in response evaluation of imatinib treated GIST patients.

First author	FDG non avid (N)	Repeat PET (N)	2nd PET	PET analysis	2nd CT	CT analysis	Clinical endpoint	Predictive value PET
Antoch [22]	NR	20	1 mo	For max 5 lesions: - sum of SUV_{max} - EORTC	1 mo	WHO[a] RECIST	NR	NR
Choi [9]	NR	40	2 mo	For all lesions: - mean SUV_{max} - ≥ 70% reduction and < 2.5 = good response	2 mo	RECIST Choi criteria	TTP[d]	Good response predicts TTP
Gayed [23]	NR	49	2 mo	For largest lesion in every organ: - SUV_{max} - adjusted EORTC	2 mo	5% change in longest diameter of largest lesion per organ	NR	NR
Goerres [16]	7	28	NR	For 1 lesion: - visual change - positive vs negative 2nd scan - SUV - adjusted EORTC	NR	RECIST	TTP[e] OS	Negative 2nd PET predicts TTP and OS
Goldstein [17][16]	1	17	2 mo	- visual response vs no response	2 mo	RECIST	NR	For clinical benefit vs PD on 2nd CT: PPV 93%, NPV 100%, FNR 50%

Table 3: continued.

First author	FDG non avid (N)	Repeat PET(N)	2nd PET	PET analysis	2nd CT	CT analysis	Clinical endpoint	Predictive value PET
Holdsworth [8]	NR	63	1 mo	For 1 lesion: - SUV_{max} - 25% reduction - 40% reduction - < 2.5 - < 3.4	1 mo	SWOG[b]	TTF[e]	All PET parameters predict TTF
Jager [4]	NR	14	1 wk	For multiple lesions: - mean SUV_{max} - % change	2 mo	RECIST OR[c]	PFS[e]	- PET response predicts PFS - For CB vs PD on CT 2nd CT: PPV 100%, FNR 21%
Stroobants [6]	2	19	1 wk	For 3 lesions: - SUV_{max} - EORTC	1 mo	RECIST	TTF[e]	- PET response predicts PFS - For CB vs PD as best response: PPV 92%, NPV 75%, FNR 8%
Van den Abbeele [14]	NR	39	1 wk	For target lesions: - background-subtracted SUV_{max} - EORTC	1 mo	RECIST	NR	For CB vs PD as best response: PPV 100% NPV 14% FNR 16%

First author	FDG non avid (N)	Repeat PET(N)	2nd PET	PET analysis	2nd CT	CT analysis	Clinical endpoint	Predictive value PET
Oosting	4	30	1 wk	For max 5 lesions: - mean SUV_{max} - mean SUV40 - mean SUV70 - EORTC - 70% reduction and < 2.5 For 1 lesion: - SUV_{max} - 25% reduction - 40% reduction - < 2.5 - < 3.4	2 mo	RECIST Choi criteria	PD at 2 mo PFS	For CB vs PD on 2nd CT (RECIST): PPV 92% FNR 11% (Choi) PPV 95% FNR 9% - No correlation between PET response and PFS

N: number of patients; SUV = standardized uptake value; NR = not reported; NA not available; mo = months, CB = clinical benefit (complete response + partial response + stable disease); PD = progressive disease; PPV = positive predictive value; NPV = negative predictive value, FNR = false negative rate; TTP = time to progression; OS = overall survival; PFS = progression free survival; TTF = time to treatment failure (failure = progression, death or treatment discontinuation)[a] WHO = World Health Organization guidelines [24].

[b] SWOG = South West Oncology Group criteria [25].

[c] OR = overall treatment response (clinical and radiological parameters and change in the rate of disease progression) [26].

[d] Progression: new lesion on CT, or new intra-tumoral nodule, or increase in size of existing intra-tumoral nodule, or overall increase in size >20% in absence of post treatment hypodense change

[e] No definition of progression

vitro that different intracellular signaling cascades are responsible for imatinib induced down-regulation of Glut4 expression and imatinib induced apoptosis in GIST cells. However, no association between reduction in Glut4 expression and reduction in FDG uptake in tumors of GIST patients treated with imatinib in the neoadjuvant setting was found [14]. Previous studies in GIST patients showed that metabolic response correlated with PFS, time to progression or time to treatment failure (i.e. disease progression or death from any cause whichever occurs first) [4,6,8,9,16].

In Table 3, the current and previous studies are summarized. We did not find a correlation between metabolic response and PFS despite testing different SUV parameters and multiple cut off values for metabolic response. This may be due to the different definitions of metabolic response that are used. EORTC criteria are based on a few small studies in which no GIST patients were included. These criteria should therefore be regarded as consensus recommendations rather than evidence based guidelines [7]. Also, adherence to EORTC FDG-PET criteria does not guarantee similar analysis, as for example the number of lesions to be assessed per patient is not defined. Furthermore, a description of how disease progression is determined, is only provided by Choi et al and differs slightly from the ESMO recommendation that we used [9,13]. Finally, the small size of these studies and the different timing of FDG-PET scans will clearly affect the results.

We found no FDG uptake in tumor lesions before start of treatment in four out of 36 patients. This corresponds with previous findings [6,16,17]. The numbers of patients are too small to draw conclusions on prognostic or predictive value of a negative baseline FDG- PET scan.

We studied metabolic response in GIST patients starting first line treatment, according to mutation. Although small numbers prohibit conclusions, the FDG-PET results for the three patients with a *PDGFRA* exon 18 mutation were striking: two patients showed non FDG-avid lesions and the third patient is the only patient with an increase in FDG uptake after 1 week imatinib treatment. This suggests that in tumors with a *PDGFRA* exon 18 mutation, metabolic response to imatinib differs from *KIT* mutated tumors. Metabolic response was seen in 85% of patients with *KIT* exon 11 mutations (23/27) and in 50% (2/4) of patients without *KIT* or *PDGFRA* mutations after 1 week imatinib [14]. Fuster et al. performed FDG-PET scans in imatinib resistant GIST patients before and after initiation of doxorubicin while continuing imatinib [18]. In 15 patients with mutation analysis available, they demonstrated lower baseline SUV_{max} in patients with wild type *KIT* tumors compared to non-wild type *KIT* tumors. However, in another second line study with sunitinib in imatinib resistant GIST patients, no correlation was found between *KIT* mutational status and metabolic activity or metabolic response in 22 patients [19].

Limitations of our study are the retrospective nature and the relative small size of the cohort. However, the data presented support the conclusion that early assessment of metabolic response with FDG-PET after 1 week of imatinib treatment in GIST patients is not helpful for go-no-go decisions. Primary imatinib resistance cannot be reliably identified with this technique. Therefore absence of progressive disease at 2 and 4 months according to RECIST 1.0 remains the most robust way to identify patients with a survival benefit from imatinib [20]. For second line

treatment with sunitinib also the absence of progressive disease according to RECIST 1.0 at 3 months seems the best way to identify patients benefiting from this treatment [21].

This does not preclude an important role for FDG-PET imaging in staging GIST patients, as FDG-PET can reveal metastases that are missed on CT [4,16,22,23].

In conclusion, the results of our study suggest that repeat FDG-PET imaging early after initiation of imatinib in patients with GIST is not informative for clinical decision making with regard to continuation of imatinib. Imatinib is an extremely effective agent for this disease and should, in the advanced setting, be continued until convincing clinical and/or radiological evidence of progressive disease or unacceptable toxicity.

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