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Very Early Detection of Response to Imatinib Mesylate Therapy of Gastrointestinal Stromal Tumours Using ^{18}Fluoro-Deoxyglucose-Positron Emission Tomography

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Abstract. *Aim: To investigate whether ^{18}F-FDG-PET allows early assessment of response to imatinib mesylate in GIST patients. Patients and Methods: Five gastrointestinal stromal tumour (GIST) patients and one patient with a KIT-positive small cell cancer were studied. Treatment consisted of 400 mg imatinib mesylate daily. ^{18}F-deoxyglucose-positron emission tomography (^{18}F-FDG-PET) scans were done before and one week after starting imatinib mesylate therapy. Results: Metabolic responses were detected after only one week of therapy in all GIST patients (four partial and one complete response). The mean decrease of the standardised uptake value was 60% (range 43 to 77%). In contrast, the tumour of the non-GIST patient was metabolically stable. Four of the 5 GIST patients achieved a partial response on CT after a mean duration of 23 weeks (range 6 to 48 weeks). Conclusion: ^{18}F-FDG-PET is a valuable method for the detection of response to imatinib mesylate in patients with KIT-positive tumours as early as one week after starting therapy.*

Gastrointestinal stromal tumours (GISTs) are the most frequent mesenchymal malignancies of the gastrointestinal (GI) tract. They are believed to arise from the same progenitor as interstitial cells of Cajal (ICC), which are the pacemaker cells of the GI-tract (1). Like ICCs most GISTs express the KIT receptor tyrosine kinase. The *KIT* proto-oncogene is mutated in more than 80% of GISTs, and these mutations lead to constitutive activation of KIT. Conventional chemotherapy and radiotherapy are ineffective in GIST patients. Imatinib mesylate is a small molecule inhibitor of the tyrosine kinases Abl, Bcr-Abl, PDGFR and KIT. It specifically interacts with the ATP binding site of these kinases, which leads to suppression of their enzymatic activity. Imatinib mesylate has a striking activity in GIST patients with unresectable or metastatic disease, leading to 54% partial responses and 30% stable disease, with generally mild toxicity (2, 3). Although most patients treated with imatinib mesylate benefit from the therapy, the mean time to objective response has been reported to be about 13 weeks. GISTs are generally very avid for glucose and can therefore be visualised efficiently by ^{18}F-deoxyglucose-positron emission tomography (^{18}F-FDG-PET). In the present study we investigated, whether ^{18}F-FDG-PET would be useful in early response evaluation of GIST patients under imatinib mesylate therapy. Therefore, five GIST patients and one non-GIST patient, whose tumours were KIT-positive, were examined. All patients received imatinib mesylate for metastatic or unresectable disease. Prior to the initiation and on day 8 of therapy, all patients were examined by ^{18}F -FDG-PET.

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Patients and Methods

Five consecutive patients had either unresectable (n=2) or metastatic (n=3) GISTs (Table I). GIST diagnosis was confirmed by strong immunohistochemical KIT expression and by detection of *KIT* mutations in exons 11 (n=4) or 9 (n=1), as described previously (4). One patient with a small cell cancer of unknown primary site which also expressed KIT was additionally included into the study as a control. After informed consent was obtained, treatment, which consisted of 400 mg of imatinib mesylate, was given daily as a single oral dose. Baseline contrast computerised tomography (CT) scans as well as follow-up investigations at weeks 4, 12, 24 and 50 were scheduled for all patients. Response in CT scans was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) (5). ^{18}F-FDG-PET studies (Ecat Exact camera biograph and PET-CT camera by Siemens) were performed 60 minutes after the injection of 200 to 370 MBq of ^{18}F -FDG after

Table I. *Patient characteristics.*

Patient number	Age (years)	Gender	Histology	Tumour site(s)	Primary tumour site	Previous treatments	*KIT* mutational status
1	72	Male	GIST	Stomach, infiltrating left liver lobe	Stomach	None	6 bp insertion at codon 504 (exon 9)
2	42	Male	GIST	Liver metastases	Small intestine	Surgical resection, chemotherapy, hyperthermia	Q556_D572del (exon 11)
3	68	Male	GIST	Peritoneal and liver metastases	Small intestine	Repeated surgical resection	V559A (exon 11)
4	53	Male	GIST	Peritoneal metastases	Stomach	Surgical resection	W557_K558del (exon 11)
5	80	Female	GIST	Oesophagus	Oesophagus	None	W557_K558del (exon 11)
6	61	Female	Small cell cancer of unknown primary Site	Liver metastases	Unknown	Chemotherapy	Wild-type exon 11

Table II. *Response evaluation.*

Patient number	Histology	Mean SUV before treatment	Mean SUV on day 8 of treatment	Change in SUV	Metabolic response on day 8 of treatment	Best response (RECIST)	Time to best response (RECIST)
1	GIST	5.15	1.2	– 77 %	CMR	PR	12 weeks
2	GIST	5.7	1.8	– 69 %	PMR	SD	n.a.
3	GIST	4.4	1.9	– 56 %	PMR	PR	50 weeks
4	GIST	8.6	1.8	– 71 %	PMR	PR	24 weeks
5	GIST	7.6	4.3	– 43 %	PMR	PR	4 weeks
6	Small Cell Cancer	11.4	12.0	+ 7 %	SD	PD	n.a.

CMR = complete metabolic response; PMR = partial metabolic response; SD = stable disease; PR = partial remission; PD = progressive disease; n.a. = not applicable

a fasting period of at least 6 hours. The emission time was 5 minutes per bed position. Attenuation correction was performed on the basis of 2-minute-transmission scans. Iterative reconstruction algorithms were used. Blood glucose levels were less than 120 mg/dl. PET scans were repeated on day 8 of treatment. Standardised uptake values (SUV) of regions of interest (ROI) defined in the initial scan were calculated and used for response evaluation. The European Organization for Research and Treatment of Cancer (EORTC) recommendations for PET response evaluation were applied (6). Complete metabolic response (CMR) was defined as a decrease of the metabolic activity of a given ROI to that of the surrounding normal tissue, *i.e.* that no more lesion was detectable on visual examination. Partial metabolic response (PMR) was defined as a decrease in SUV of at least 25%. Stable disease (SD) was defined as either a decrease or an increase of the SUV of less than 25%. Progressive metabolic disease (PMD) was defined as an increase of the SUV by at least 25%. Statistical analysis was performed using the paired *t*-test. *P*-values are two-tailed.

Results

All but one patient (#5) were able to take imatinib mesylate as prescribed (400 mg/day). Patient #5 had to pause for 3 days due to abdominal discomfort but continued therapy from day 6 onwards.

PET response. All GIST-patients showed a striking uptake of ^{18}F-FDG before starting imatinib mesylate therapy, and the mean SUV in the GIST lesions was 5.7 (range 4.4 to 7.6). After 1 week of therapy, one GIST patient had a complete metabolic response, and the other four GIST patients had a partial metabolic response with a mean decrease in SUV of 60% (range 43 to 77%). The mean SUV after therapy decreased to 2.2 (range 1.2 to 4.3) (Table II). The difference between the two groups was significant

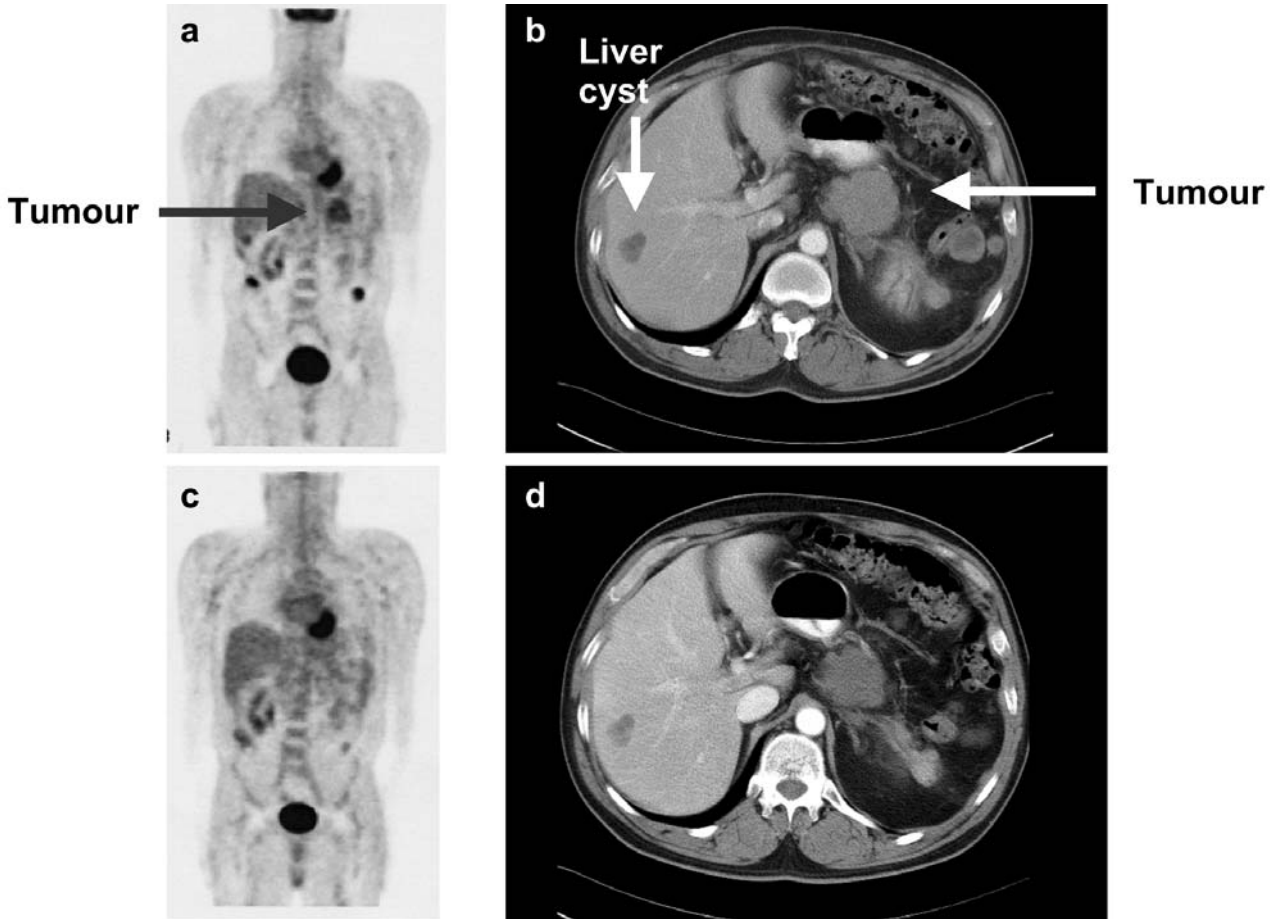

Figure 1. *^{18}F-FDG-PET and CT scans of patient #4. ^{18}F-FDG-PET scans before and on day 8 of imatinib mesylate therapy (a and c, respectively) as well as CT scans before and 4 weeks after beginning the imatinib mesylate therapy (b and d, respectively). Note that on ^{18}F-FDG-PET the major lesion in the left upper abdomen had completely disappeared, and only minor foci could be detected in both lower quadrants. In contrast, on the CT scan the major lesion in the upper abdomen showed only a minor shrinkage. The liver cyst shown is benign.*

(p=0.0049) Patient #6, the patient with a KIT-positive small cell carcinoma, had a metabolically stable disease with a mean increase in SUV of 7%. Interestingly, patient #5 showed a decrease in SUV of 43%, although she only was able to take 57% of the intended dose.

CT response. Four of the five GIST patients achieved a partial response according to RECIST after a mean of 23 weeks (range 4 to 50 weeks) of therapy (Table II). The other GIST patient had a morphologically stable disease. Typically, GIST lesions became cystic in appearance, as early as 4 weeks after initiation of imatinib mesylate therapy. Therefore, liver metastases became more detectable. The only non-GIST patient in the study did not respond to imatinib mesylate therapy, as confirmed by both PET and CT scans, and the tumor rapidly progressed.

Discussion

Impressive response rates have been achieved in patients treated with imatinib mesylate for unresectable or metastatic GIST. However, the mean time to objective tumor shrinkage, as evidenced by CT scan, has been reported to be approximately 13 weeks. Our data show that a metabolic response, as assessed by ^{18}F-FDG-PET, to imatinib mesylate therapy can be detected as early as 1 week after the initiation of therapy (see Figure 1 for an example). In contrast, the time to objective tumor shrinkage according to RECIST was 23 weeks. One patient (#2), although having a reduction in SUV of 69% and improving clinically, never reached a partial response according to RECIST. Instead, the tumour lesions became necrotic, as evidenced by a homogeneously reduced density in CT scan, but remained stable in size for more

than 2 years. Thus, in this case, PET response predicted the patient's long-term benefit better than the response evaluation according to RECIST.

Our results are in accordance with those obtained by Stroobants and coworkers, who reported 17 GIST and 4 non-GIST soft tissue sarcoma (STS) patients who they treated with 400 mg imatinib mesylate and who were examined by ^{18}F-FDG-PET prior to and on day 8 of imatinib mesylate therapy (400 mg/day) (7). These authors found 11 complete and 2 partial metabolic responders. Stable or progessive metabolic disease was observed in 8 patients including the 4 non-GIST STS patients. Eight out of 10 PET responders were also subsequent responders on CT. Other groups compared ^{18}F-FDG-PET with CT in GIST patients under imatinib mesylate therapy at later time-points, ranging from 1 month up to 6 months after the start of treatment. They found a good correlation of PET and CT responses (8-11). In agreement with our findings, PET responses always preceded responses on CT by several weeks. We conclude that PET is an appropriate method for the very early evaluation of response to imatinib mesylate therapy in KIT-positive tumours such as GISTs.

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