PERGAMON

European Journal of Cancer 39 (2003) 2012–2020

European Journal of Cancer

www.ejconline.com

^{18}FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec®)

S. Stroobants[a,*], J. Goeminne[b], M. Seegers[b], S. Dimitrijevic[c], P. Dupont[a], J. Nuyts[a], M. Martens[b], B. van den Borne[b], P. Cole[c], R. Sciot[d], H. Dumez[b], S. Silberman[c], L. Mortelmans[a], A. van Oosterom[b]

[a]*Department of Nuclear Medicine, UZ Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[b]*Department of Oncology, University Hospital Gasthuisberg, Leuven, Belgium*
[c]*Novartis Oncology, Novartis Pharma AG, Basel, Switzerland, and Novartis Pharmaceuticals, East Hanover, NJ, USA*
[d]*Department of Pathology, University Hospital Gasthuisberg, Leuven, Belgium*

Received 15 January 2003; accepted 15 January 2003

Abstract

Imatinib mesylate (Glivec®, formerly STI571) is the first effective systemic treatment for gastrointestinal stromal tumours (GISTs). Major changes in tumour volume, however, tend to occur late after the start of treatment. The aim of this study was to evaluate if [^{18}F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) can be used for the early evaluation of response to imatinib mesylate treatment in soft-tissue sarcomas (STS). 21 patients (17 GIST, 4 other STS) underwent FDG-PET imaging prior to and 8 days after the start of treatment. PET response (European Organization for Research and Treatment (EORTC) guidelines) was observed in 13 GISTs (11 Complete Responders, 2 partial responders. Subsequent computerised tomography (CT) response Response Evaluation Criteria in Solid Tumours (RECIST) was observed in 10 of these patients after a median follow up of 8 weeks. Stable or progressive disease was observed on PET in 8 patients and none of them achieved a response on CT. PET response was also associated with a longer progression-free survival (PFS) (92% versus 12% at 1 year, $P = 0.00107$). We conclude that FDG-PET is an early and sensitive method to evaluate an early response to imatinib treatment.

Keywords: Positron emission tomography; Fluorodeoxyglucose; Imatinib mesylate; c-kit; Receptor protein-tyrosine kinase; Gastrointestinal stromal tumour; Soft-tissue sarcoma

1. Introduction

Traditionally, the response to cancer treatment in solid tumours is evaluated by subsequent clinical or radiological assessments of target lesions and is defined as a significant decrease in measurable tumour dimensions [1,2]. There are, however, important limitations to the evaluation of tumour response by volume changes, especially in soft-tissue sarcomas (STS). Accurate measurement of tumour dimensions can be extremely difficult in non-well defined lesions like bone, bowel or peritoneal metastases. Reduction in the viable tumour cell fraction does not always result in a volume reduction since tumour tissue can be replaced by necrotic or fibrotic tissue and morphological images are unable to differentiate between these different tissue types. Furthermore, volume changes are rather late events. Usually, the first evaluation of objective responses measured by computerised tomography (CT) are performed not earlier than 2–3 months after the start of treatment because earlier changes are seldom significant. Therefore, patients are often unnecessarily exposed to ineffective, poorly tolerated, toxic or expensive treatments during a prolonged time. Finally, the new antivascular and cytostatic agents aim at tumour growth stabilisation rather than tumour shrinkage and

* Corresponding author. Tel.: +32-16-343714; fax: +32-16-343759.
E-mail address: sigrid.stroobants@uz.kuleuven.ac.be (S. Stroobants).

0959-8049/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0959-8049(03)00073-X

thus no major volume changes are to be expected. To evaluate treatment efficacy, other criteria for response assessment need to be defined.

In recent years, metabolic imaging with positron emission tomography (PET) has become increasingly important in cancer management. The most frequently used radiotracer is [^{18}F]-fluorodeoxyglucose, (FDG), a glucose analogue that is preferentially 'trapped' in fast-metabolising cells, such as those in malignant tumours [3]. Initially, FDG-PET was used in the diagnosis and staging of malignancies [4,5], but, more recently, promising results have also been obtained in the evaluation of the response to treatment [6–12]. Because glucose provides the primary source of carbons for the *de novo* synthesis of nucleic acids, lipids and amino acids, FDG uptake, a marker of the glucose metabolism is closely related to the number of viable cells [13] and the proliferation capacity of these cells [14]. Treatment-induced changes resulting in tumour cell death or growth arrest should therefore result in a subsequent reduction in FDG uptake, making this technique a sensitive and early marker of response. A number of small clinical trials have indeed indicated that quantification of changes in FDG uptake may provide an early and sensitive pharmacodynamic marker of the cytotoxic or cytostatic effect of anticancer drugs and result in improved monitoring of tumour response to anticancer drugs at a clinical and sub-clinical level as previously described by the European Organization for Research and Treatment of Cancer (EORTC) PET study group [15].

In this study, we examined the value of FDG-PET in the assessment of early tumour response to therapy with imatinib mesylate (Glivec®, formerly STI571, Novartis Pharma AG, Basel, Switzerland) in patients with different STS. Imatinib mesylate is an oral, bio-available, small molecule, that is an inhibitor of certain receptor tyrosine kinases involved in cell signalling, including KIT [16]. Gastrointestinal stromal tumours (GISTs) are rare neoplasms that are thought to arise from the mesenchymal cells of the gastrointestinal tract. The majority of GISTs are characterised by mutations in the *KIT* gene, which can cause a ligand-independent activation of its tyrosine kinase function and play a critical role in tumorigenesis, by promoting tumour growth and preventing apoptosis [17,18]. Inhibition of this KIT-driven growth pathway by imatinib mesylate has shown very promising clinical results in the treatment of patients with advanced GISTs, which are highly refractory to chemotherapy [19–21]. Although most patients experienced major and rapid symptom relief, objective tumour response as evaluated by anatomical imaging (CT or magnetic resonance imaging (MRI)) occurred often only after several months. Therefore, the aim of this study was to evaluate if metabolic imaging using FDG-PET can be used for the earlier and more sensitive evaluation of the response of STS to treatment with imatinib mesylate.

2. Patients and methods

2.1. Patients

All patients from the University Hospital Gasthuisberg, included in the phase I/II trial of the EORTC-STBSG (Soft Tissue and Bone Sarcoma Group study) investigating the maximum tolerated dose (MTD) (phase I) and efficacy (phase II) of imatinib mesylate in the treatment of advanced STS, were also prospectively evaluated using a PET protocol. The protocol had been approved by the EORTC New Treatment Committee, the EORTC Protocol Review Committee and the local Medical Ethics Committee. All patients entering the phase I or II study had to have histological confirmation of STS and for the diagnosis of GISTs, positive c-kit expression on the basis of CD117 immunohistochemical staining. Furthermore, they had to have a measurable lesion, with evidence of progression within 6 weeks prior to treatment. Previous chemotherapy was allowed, but had to have been discontinued for at least 4 weeks before the study start. Before patient registration, informed consent had to be given according to ICH/European Union-Good Clinical Practice (EU-GCP) guidelines, and national-local regulations. Within 14 days prior to treatment, a full evaluation, including medical history, physical examination, performance status assessment, full haematology, blood chemistry, urine analysis, chest X-ray and clinical tumour measurements by CT scan were performed.

2.2. Treatment

Patients included in the phase I dose-finding study received imatinib mesylate in doses ranging from 400 mg once daily (o.d.) to 500 mg twice daily (b.d.) whereas patients included in the phase II study were treated at the MTD defined at 400 mg b.d. [20].

Treatment was administered until progression of the disease, unacceptable toxicity or patient refusal. In the case of disease stabilisation and the absence of unacceptable side-effects, treatment was allowed to continue for a minimum of 1 year. In cases of objective complete or partial response, treatment was to be continued until documented disease progression or for at least one year after the documentation of a complete response.

2.3. Evaluation of tumour response

The objective tumour response was measured by serial CT scanning. Target lesions were re-evaluated 4 and 8 weeks after the start of treatment and every 8 weeks thereafter. CT scan was performed earlier in cases of clinical suspicion of progression. Responses were classified according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria [2]. All responses

had to be confirmed by repeated imaging within 4–8 weeks. Time to treatment failure was defined as the time from the first dose of imatinib mesylate to the earliest occurrence of progression, death from any cause, or withdrawal from the trial for any reason other than that the condition no longer required therapy.

Subjective tumour response, defined as a change in tumour-related symptoms, was evaluated by the taking down of the patient's history and clinical examination weekly for the first 8 weeks, biweekly until week 12, and monthly thereafter.

2.4. FDG-PET

All patients included in the PET sub-study protocol of the phase I-II study underwent FDG-PET imaging before and 8 days after the start of imatinib mesylate treatment. PET imaging was repeated at day 28 and every 8 weeks thereafter until a complete metabolic remission was achieved. In a limited number of patients, additional PET studies at earlier time points were performed (24 or 48 h after the start of treatment). Patients were excluded for PET follow-up in cases of insufficient FDG uptake in the target lesions at their baseline PET scan.

PET imaging was performed on a CTI-HR + scanner (Siemens-CTI, Knoxville, USA) with an axial field of view of 15 cm and a resolution of approximately 8 mm. All patients fasted for at least 6 h. 60 min after the injection of 6 MBq/kg FDG, an attenuation-corrected whole body scan was acquired in seven bed positions (5-min emission and 3-min transmission). All data were corrected for decay and photon attenuation and reconstructed with an iterative reconstruction algorithm [22]. Transaxial, coronal and sagital images were used for the image analysis. Besides the visual interpretation to assess the appearances of new lesions, the maximum standardised uptake value (SUV_{max}) was calculated for the different target lesions [23]. Target lesions were defined as the three tumour lesions with the highest FDG uptake on the baseline PET. Response on PET was defined according to the recommendations of the EORTC-PET group [15] (Table 1). PET was never used to change patient management. Response on PET was correlated with subjective symptom control and objective CT response. PET response was also correlated with treatment outcome (progression-free survival (PFS)) using the Kaplan–Meier method; groups were compared with the log-rank test.

Table 1
PET response defined according to the EORTC PET recommendations [15]

CR	FDG uptake in all lesions comparable to background activity
PR	>25% decrease of SUV in all target lesions
SD	Changes in SUV of less than 25%
PD	>25% increase of SUV in at least one target lesion or the appearance of new lesions (regardless of the SUV changes in the target lesions

EORTC, European Organization for Research and Treatment of Cancer; PET, positron emission tomography; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SUV, standardised uptake value.

3. Results

3.1. Patients

24 STS patients, enrolled in one of the two EORTC trials, were included in the PET sub-study. Histology was GISTs in 19 patients, fibrosarcomas in 2, synovial sarcomas in 2 and leiomyosarcoma in 1 patient. Baseline PET showed high FDG uptake in 17/19 GISTs and moderate to high uptake in 4/5 of the other sarcomas. 3 patients (two GISTs, one synovial sarcoma) were excluded for PET follow-up because the tumour was not FDG avid. Therefore, 21 patients were available for further analysis and their characteristics are given in Table 2.

3.2. CT response

In the four non-GISTs, no durable responses were obtained: 3 patients showed early progression within 1

Table 2
Characteristics of the patients available for PET follow up

Characteristic	All patients ($n=21$)
Age (years)	
Median (range)	55 (38–70)
Gender	
Male	12
Female	9
Study type	
Phase I	14
Phase II	7
Histology	
GIST	17
Fibrosarcoma	2
Leiomyosarcoma	1
Synovial sarcoma	1
Imatinib dose at the start of treatment	
1*400 mg	2
2*300 mg	2
2*400 mg	12
2*500 mg	5
FDG uptake prior to treatment	
GIST	
Mean SUV of all target lesions (range)	11.3 (5.6–24.8)
Other STS	
Mean SUV all target lesions (range)	4.8 (2.1–11.1)

PET positron emission tomography; GIST, gastrointestinal stromal tumour; FDG, [^{18}F]-fluorodeoxyglucose; STS, soft-tissue sarcoma.

month after the start of treatment, 1 patient progressed after 21 weeks.

In the GIST patients, a partial response was observed in 10/17 (59%), with a median reduction in tumour size of 59% (S.D. 14, range 30–82%). The time to reach a partial response was highly variable with a median of 8 weeks (range 4–48 weeks). A durable stable disease for more than 1 year was obtained in 3 GIST patients whereas early disease progression was noted in 4 GIST patients after a median treatment time of 5 weeks (range 2–21 weeks).

The time to treatment failure for all patients is given in Fig. 1a. All GIST patients who reached at least stable disease (13/17 patients or 76%) are still treated with imatinib mesylate after a median follow-up of 84 weeks (range 57–89 weeks). 4 of them (1 with initial stable and 3 with responding disease) progressed after 64–88 weeks

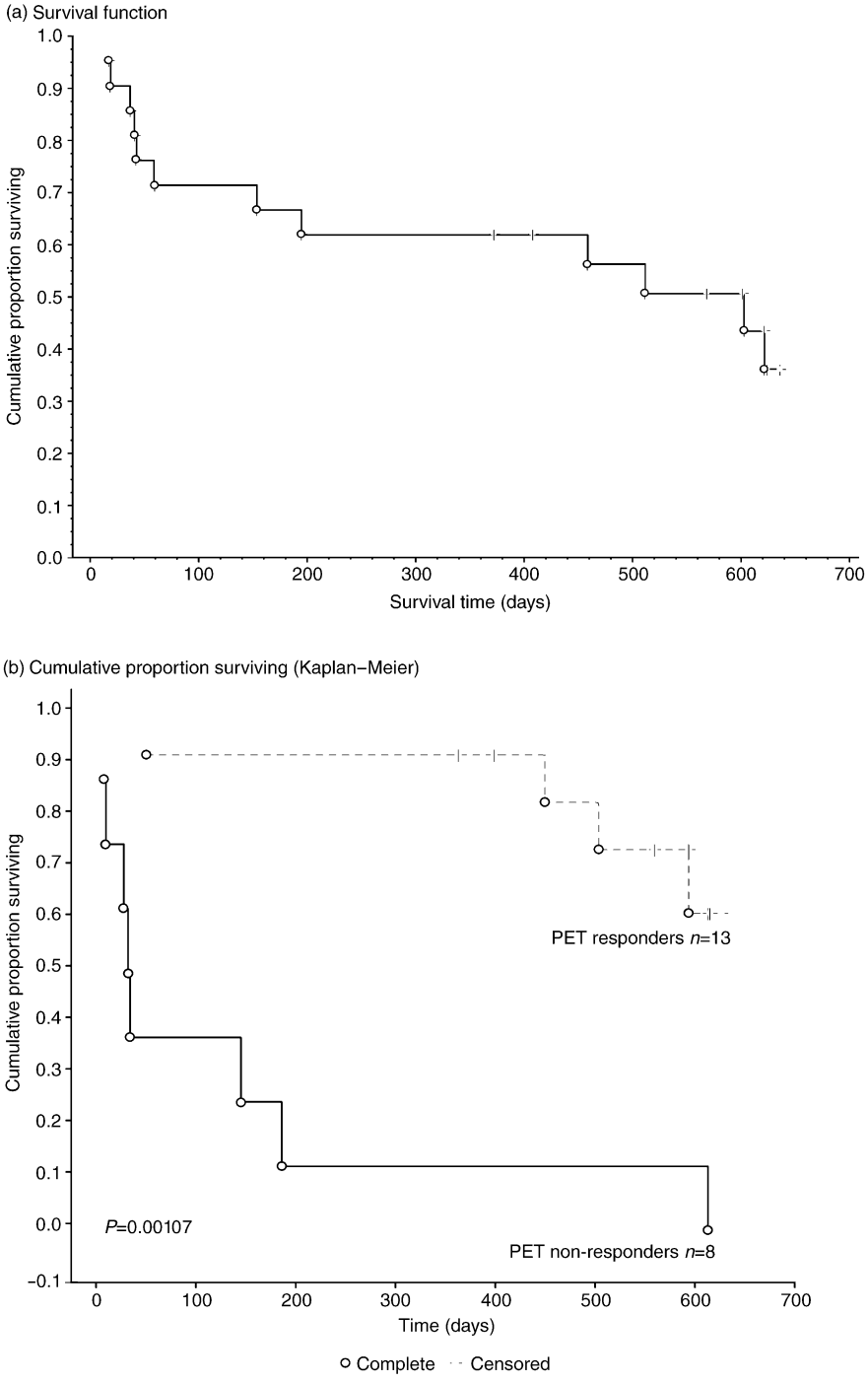

Fig. 1. Kaplan–Meier survival curves of time to treatment failure in all patients (a) and according to positron emission tomography (PET) response (b).

of treatment, but reached stable disease again after a dose escalation.

3.3. Subjective tumour response

Tumour-related symptoms were present in all of the other STS and in 11/17 of the GIST patients. Already after one week of imatinib mesylate intake, major symptom relief was observed in 6/11 GIST patients. Treatment efficacy was later confirmed by a subsequent partial response on CT in 5 patients and a durable stable disease in 1 patient. A further deterioration of the performance status was seen in four GISTs and in all of the other STS and all of them also showed early progression on CT. In 1 patient, the abdominal complaints remained, but changed (i.e. less pain, more nausea), a partial response was later observed on CT.

6 GIST patients were and remained symptom-free during the first months of treatment. 4 of these patients achieved a partial response and 2 a durable stable disease on CT.

3.4. PET response

3.4.1. After 8 days of treatment

Of the 4 non-GISTs patients, none achieved a response on PET. An example is given in Fig. 2. Of the 17 GIST patients, 11 achieved a complete remission. An example is given in Fig. 3. Two patients obtained a partial response with a reduction in SUV_{max} of 80% and 30% respectively. On a repeat PET scan at day 28, the patient with the initial major response obtained a complete remission, whereas no further decline in FDG uptake was seen in the patient with initial minimal response. No change in FDG uptake from baseline was seen in 1 GIST patient on serial PET scanning performed between 8 days and 56 weeks of treatment. Finally, disease progression on PET at day 8 was observed in 3 GIST patients. For correlation of PET responses with subjective and objective CT responses and PFS, the PET response obtained at day 8 will be used in any further analyses.

3.4.2. After 24–48 h of treatment

In 5 patients, an additional PET scan 24–48 h after the start of treatment was undertaken. Early PET response always predicted the response on PET at day 8. In 2 of the patients, a major decrease in SUV_{max} was observed (−53%, −67%) and both reached CR on PET at day 8 (Fig. 4). In the other 3 patients, no major change ($n=1$) or disease progression ($n=2$) was observed at 24 or 48 h. On PET scan at day 8, all 3 showed progressive disease.

3.4.3. Correlation of the PET response and symptom control

The PET response was closely related to symptom control. All of the 6 patients who showed a major reduction in tumour-related complaints reached a complete ($n=5$) or major ($n=1$) metabolic response, while those with a deterioration in their performance status ($n=8$) also showed progressive disease on PET in all, but 1, patient (minimal response on PET).

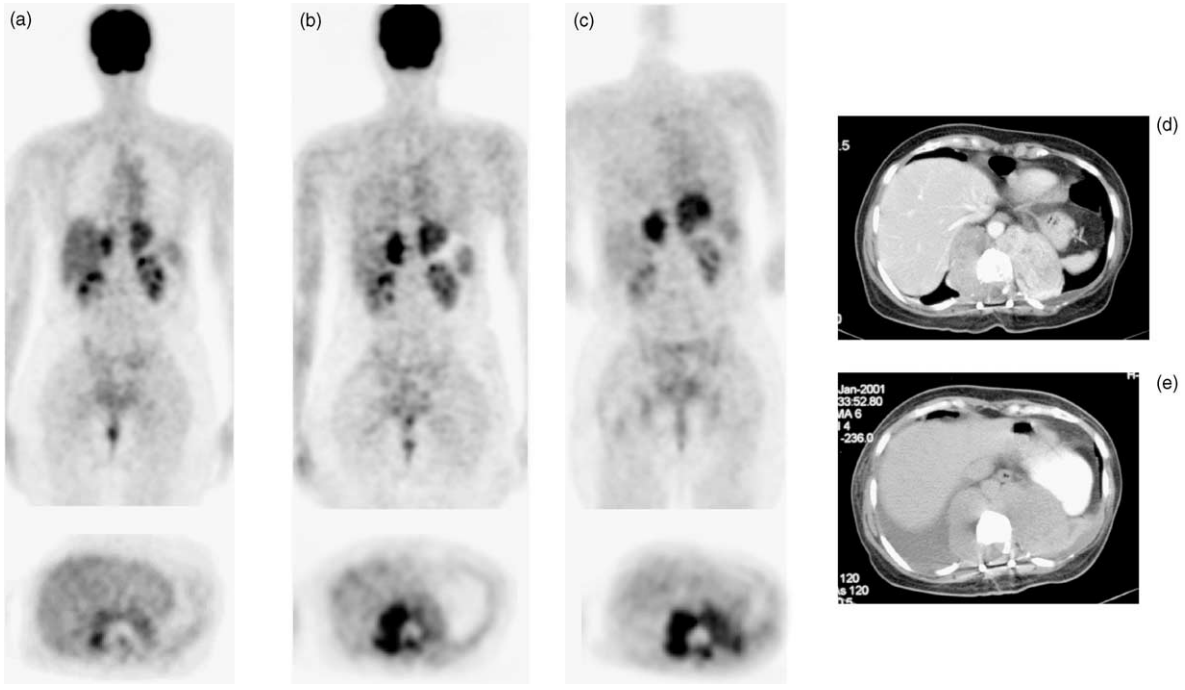

Fig. 2. Leiomyosarcoma with a metastatic mass around the vertebral spine prior to the start of treatment on positron emission tomography (PET) (a) and computerised tomography (CT) (d). On PET at day 8 progressive disease was observed (b) and this was confirmed by PET (c) and CT (e) after 1 month of treatment.

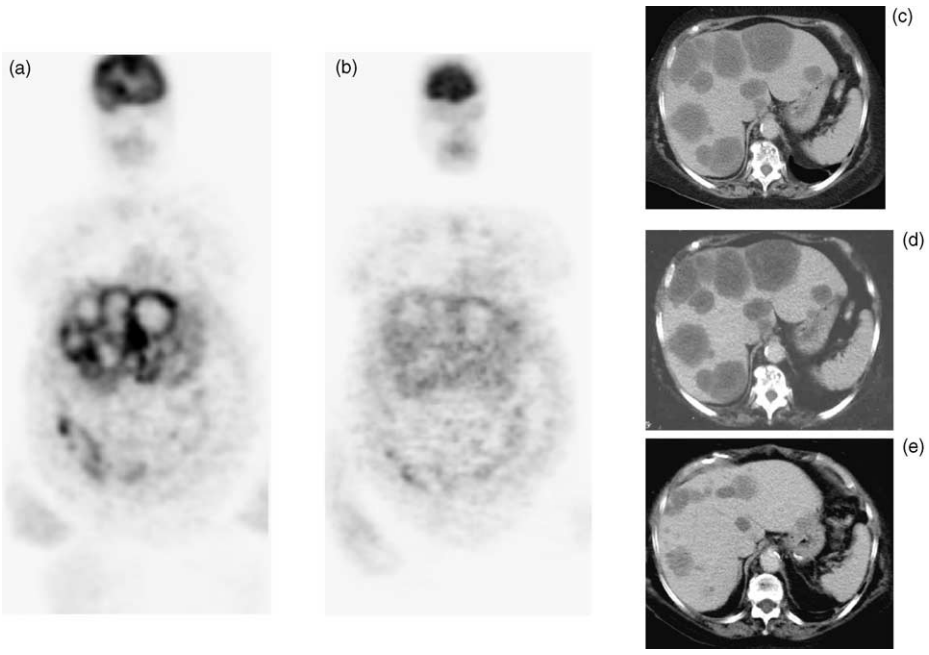

Fig. 3. GIST patient with multiple liver and peritoneal metastases prior to the start of treatment on positron emission tomography (PET) (a) and computerised tomography (CT) (c). A complete remission was achieved on PET 8 days after the start of imatinib treatment (b). On CT at 4 weeks, no major volume changes were observed (d). Only after 24 weeks of treatment (e) was an objective tumour response observed on CT.

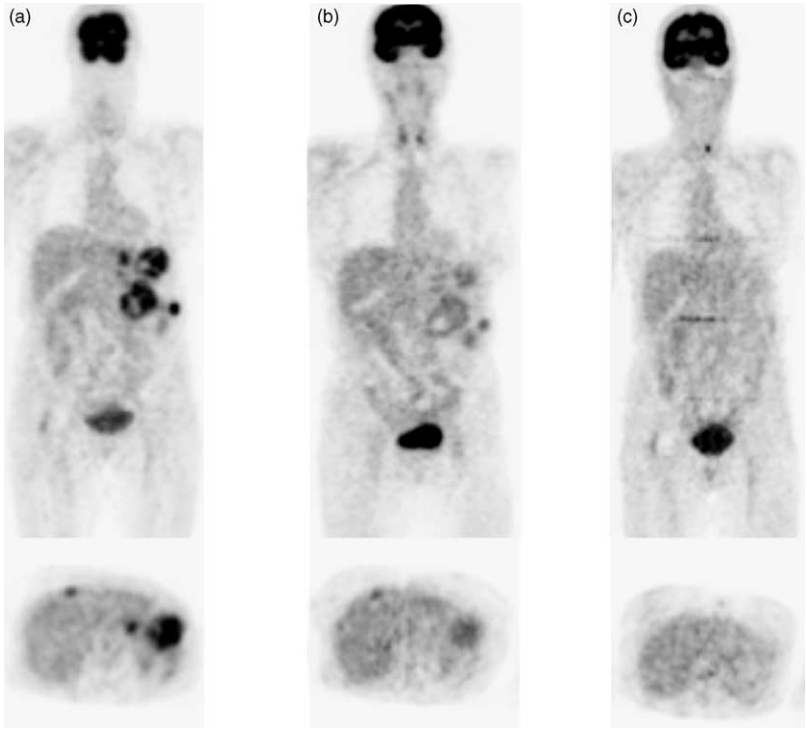

Fig. 4. GIST patient with multiple abdominal metastases on positron emission tomography (PET) prior to treatment (a). A major reduction in [^{18}F]-fluorodeoxyglucose (FDG) uptake at 48 h after the start of treatment was observed (b), and correctly predicted the achievement of a complete remission on PET at day 8 (c).

3.4.4. Correlation of the PET and CT responses (Table 3)

PET response correctly predicted CT response in 18/21 patients. All patients with a complete or major metabolic response subsequently reached a partial ($n=10$) or durable stable disease ($n=2$) on CT and the PET response preceded CT response by a median of 7 weeks (range 4–48 weeks). All patients with progressive disease on PET ($n=6$) also showed progressive disease on CT. Only for patients with stable disease or minimal

Table 3
Overview of all PET responses and subsequent CT responses

PET response	Patients (*n*)	GIST/ other STS	Best CT response		
			Partial	Stable	Progression
Complete	11	11/0	9	2	
Partial	2	2/0	1		1
Stable	2	1/1		1	1
Progression	6	3/3			6

PET, positron emission tomography; CT, computerised tomography; GIST, gastrointestinal stromal tumour.

metabolic responses is the subsequent CT response less predictable (durable stable disease or progression in 1 and 2 patients, respectively.

3.4.5. Correlation of the PET response and progression-free survival (PFS) (Fig. 1b)

Survival analysis revealed a significantly better PFS in the PET responders with a 1-year PFS survival rate of 92% compared with only 12% in the non-responders ($P = 0.00107$). In patients with at least a major metabolic response, only late relapses were observed, while the patient with minimal response progressed early after the start of treatment.

4. Discussion

Metabolic imaging with FDG-PET seems to be an excellent tool to evaluate treatment efficacy in STS patients treated with imatinib. A complete metabolic response was achieved within 1 week in most of the responding patients (all GISTs) and preceded CT response by several weeks. Furthermore, early metabolic response was associated with a significant longer PFS ($P = 0.00107$).

The better understanding of the pathophysiology of different cancer types has led to the development of a whole new class of anti-cancer drugs; the protein tyrosine kinase inhibitors (PTKI) [24]. Imatinib mesylate is the first small molecule PTKI that has been successfully introduced into human clinical practice and has now been approved for the treatment of chronic myeloid leukaemia (CML) and unresectable and/or metastatic GISTs. Early clinical trials in GISTs conducted in Europe and the United States show a significant improvement in PFS and overall survival compared with historical controls [20,21]. Although subjective tumour response occurred within a few days of treatment in responding patients, objective tumour shrinkage was minimal and tended to occur only after several weeks [19–21]. Tumour biopsies taken within 1 month after the start of treatment in some patients, showed a myxoid degeneration of the tumour with only a few foci of viable GIST cells remaining, proving the underestimation of the true response as measured by CT [19,21]. The superiority of the metabolic response assessment with FDG-PET was first reported by Joensuu and colleagues [19] in the first GIST patient ever treated with imatinib mesylate. Although the liver metastasis became 'cyst-like' on CT already 4 weeks after the start of treatment, suggesting structural and functional changes in the tumour mass, major tumour shrinkage was only achieved after 8 months of treatment. On FDG-PET, however, all hypermetabolic lesions became totally inactive after 1 month of treatment. The value of FDG-PET was later confirmed in the reports of the early clinical trials [20,21]: metabolic responses occurred early after the start of treatment and predicted the subsequent CT response. In most of these reports, PET results were only briefly reported since treatment safety and objective radiological response was the primary endpoint. In this report, we specifically focused on the PET results.

Prior to the start of imatinib mesylate treatment, moderate to high FDG uptake was observed in 17/19 GIST patients and in 4/5 of the other STS. The mean SUV of the target lesions was clearly higher in GISTs compared with the other histological subtypes (SUV_{max} of 11.3 and 4.8, respectively). Especially in GISTs, a very high range in FDG uptake (SUV_{max} ranging from 5.6 to 24.8) was observed. Folpe and colleagues [25] already described a close relationship between FDG uptake and tumour cellularity and the number of mitotic figures per high power field in a variety of bone and STS. Probably this is also the case in GISTs, but larger patient numbers are needed to explore this relationship further.

In 3 patients, of whom 2 were GISTs, no FDG uptake was observed in the known CT lesions. Therefore, a pretreatment PET scan is mandatory to evaluate the response to imatinib mesylate treatment. It is unclear why these tumours were not FDG avid since a moderate to high number of mitotic figures was seen on the histopathology.

Although clear guidelines are available for radiological response assessment [1,2], criteria for metabolic response evaluation are still not fully agreed upon. The only 'official' guidelines available to date are these of the EORTC-PET group and are based on the reproducibility of the technique [15]. FDG changes of more than 25% from baseline cannot be attributed to the imprecision of the technique and are therefore regarded as true changes in tumour glucose metabolism. Using this cut-off point, a correct discrimination between responders and non-responders to imatinib mesylate treatment could be made in most of the patients in this study. One patient with stable disease on PET obtained a durable stable disease on CT for 88 weeks. Maybe this patient had a slowly-growing GIST since the time interval

between the first diagnosis and the development of liver metastasis was more than 5 years. In contrast, one patient with a marginal reduction in FDG uptake showed early progression on radiological imaging. Retrospectively, the optimal cut-off point should probably be much more stringent since only patients with major partial responses truly benefit from this new treatment. Van den Abbeele and colleagues [26] analysed their data accordingly and found that major PET responses (residual SUV_{max} <2.5 for all lesions) were associated with a better PFS and overall survival.

In cytotoxic treatment regimens, reductions in glucose metabolism can already be seen after one cycle of chemotherapy [6,8,9] and this gradually declines with further effective treatment [10,11]. In contrast to this continuous reduction in FDG uptake during cytotoxic treatment, a rapid and almost complete shutdown of the glucose metabolism is observed almost immediately after the start of imatinib mesylate treatment in advanced GIST patients. The molecular mechanisms responsible for this rapid decrease in glycolytic activity remain unknown. One possible explanation could be a direct inhibition of the hexokinase activity by imatinib mesylate as suggested by Boren and colleagues [27]. In that case, response assessment with FDG-PET is only measuring one of the downstream effects of the blockade of the c-kit receptor rather than being a direct marker of cell viability or proliferation. This hypothesis should be further evaluated by using not only FDG, but also thymidine analogues like Fluoro-L-Thymidine (FLT) for measuring *in vivo* DNA synthesis in these patients during imatinib mesylate treatment.

We conclude that FDG-PET imaging can be used as an early and sensitive method to evaluate the response of STS to imatinib mesylate treatment. Response on PET closely correlates with subjective symptom control, precedes tumour shrinkage by several weeks and is associated with a longer PFS.

Early assessment of treatment efficacy is probably less crucial in the treatment of metastatic GIST patients, since no other effective drug is available to date. It can, however, help in identifying response in patients with ambiguous CT changes or in cases of discordant findings between subjective and CT response data. However, if imatinib treatment is expanded to the neo-adjuvant setting, early accurate assessment of response is crucial to select patients who will benefit from this neo-adjuvant treatment prior to surgery.

Acknowledgements

The authors want to thank colleagues from the radiopharmacy for their supply of FDG, the nurses and technologists from the PET for the patient studies and S. Vleugels for his technical support. We also want to thank the trial nurses for collecting the CT and outcome data, and Peter Vermaelen for the quantitative analysis of the PET data. This study was supported, in part, by a grant from Novartis Oncology, Novartis Pharma AG, Basel, Switzerland.

References

1. WHO. *Handbook for Reporting Results of Cancer Treatment. Offset Publication No. 48*. Geneva, Switzerland, World Health Organization, 1979.
2. Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000, **92**, 205–216.
3. Pauwels EK, McCready VR, Stoot JH, *et al*. The mechanism of accumulation of tumour-localising radiopharmaceuticals. *Eur J Nucl Med* 1998, **25**, 277–305.
4. Bomanji JB, Costa DC, Ell PJ. Clinical role of positron emission tomography in oncology. *Lancet Oncol* 2001, **2**, 157–164.
5. Hustinx R, Benard F, Alavi A. Whole-body FDG-PET imaging in the management of patients with cancer. *Semin Nucl Med* 2002, **32**, 35–46.
6. Wahl RL, Zasadny K, Helvie M, *et al*. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J Clin Oncol* 1993, **11**, 2101–2111.
7. Schelling M, Avril N, Nahrig J, *et al*. Positron emission tomography using Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 2000, **18**, 1689–1695.
8. Smith IC, Welch AE, Hutcheon AW, *et al*. Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. *J Clin Oncol* 2000, **18**, 1676–1688.
9. Romer W, Hanauske AR, Ziegler S, *et al*. Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose. *Blood* 1998, **91**, 4464–4471.
10. Brucher BL, Weber W, Bauer M, *et al*. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. *Ann Surg* 2001, **233**, 300–309.
11. Vansteenkiste JF, Stroobants SG, De Leyn PR, *et al*. Potential use of FDG-PET scan after induction chemotherapy in surgically staged IIIa-N2 non-small-cell lung cancer: a prospective pilot study. The Leuven Lung Cancer Group. *Ann Oncol* 1998, **9**, 1193–1198.
12. Weihrauch MR, Re D, Scheidhauer K, *et al*. Thoracic positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood* 2001, **98**, 2930–2934.
13. Higashi K, Clavo AL, Wahl RL. Does FDG uptake measure proliferative activity of human cancer cells? In vitro comparison with DNA flow cytometry and tritiated thymidine uptake. *J Nucl Med* 1993, **34**, 414–419.
14. Minn H, Joensuu H, Ahonen A, *et al*. Fluorodeoxyglucose imaging: a method to assess the proliferative activity of human cancer in vivo. Comparison with DNA flow cytometry in head and neck tumors. *Cancer* 1988, **61**, 1776–1781.
15. Young H, Baum R, Cremerius U, *et al*. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer* 1999, **35**, 1773–1782.
16. Buchdunger E, Cioffi CL, Law N, *et al*. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther* 2000, **295**, 139–145.

17. Rubin BP, Singer S, Tsao C, *et al*. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res* 2001, **61**, 8118–8121.
18. Singer S, Rubin BP, Lux ML, *et al*. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. *J Clin Oncol* 2002, **20**, 3898–3905.
19. Joensuu H, Roberts PJ, Sarlomo-Rikala M, *et al*. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001, **344**, 1052–1056.
20. van Oosterom AT, Judson I, Verweij J, *et al*. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001, **358**, 1421–1423.
21. Demetri GD, von Mehren M, Blanke CD, *et al*. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002, **347**, 472–480.
22. Shepp L, Vardi L. Maximum likelihood reconstruction for emission tomography. *IEEE Trans Med Imag* 1982, **1**, 113–122.
23. Hoekstra CJ, Hoekstra OS, Stroobants SG, *et al*. Methods to monitor response to chemotherapy in non-small cell lung cancer with 18F-FDG PET. *J Nucl Med* 2002, **43**, 1304–1309.
24. Levitzki A. Protein tyrosine kinase inhibitors as novel therapeutic agents. *Pharmacol Ther* 1999, **82**, 231–239.
25. Folpe AL, Lyles RH, Sprouse JT, *et al*. (F-18) fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. *Clin Cancer Res* 2000, **6**, 1279–1287.
26. Van den Abbeele AD, for GIST Collaborative PET Study Group. F18-FDG-PET provides early evidence of biological responses to STI571 in patients with malignant gastrointestinal stromal tumours. *ASCO*, 2001 (abstr 1444).
27. Boren J, Cascante M, Marin S, *et al*. Gleevec (STI571) influences metabolic enzyme activities and glucose carbon flow toward nucleic acid and fatty acid synthesis in myeloid tumor cells. *J Biol Chem* 2001, **276**, 37747–37753.