

Positron emission tomography in patients with aggressive fibromatosis/desmoid tumours undergoing therapy with imatinib

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Abstract

Purpose We used ^{18}F -FDG PET to evaluate the FDG uptake in patients with aggressive fibromatosis (AF, also known as desmoid tumours) undergoing therapy with imatinib (imatinib mesylate, Glivec).

Methods The pilot study included nine patients with progressive AF receiving oral treatment with imatinib at a daily dose of 800 mg. Patients were examined using PET prior to the start of therapy and during imatinib treatment. Restaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) was performed in parallel using CT and/or MRI and served as reference.

Results The clinical outcomes in nine evaluable patients were as follows: seven patients with stable disease, and two patients with progressive disease. A 27% decrease in the median average standardized uptake value (SUV) of the sequential PET examinations was demonstrated in all evaluable patients with three patients (33%) showing a decrease in SUV of more than 40% (48%, 52% and 54%, respectively); no patient showed a substantial increase in SUV.

Conclusion To our knowledge, this is the first series of AF patients undergoing treatment with imatinib and monitored using sequential PET imaging, that allows detection of

SUV changes after imatinib induction, thus helping to decide whether treatment should be continued or not.

Keywords Aggressive fibromatosis · Desmoid tumours · Fluorodeoxyglucose · Imatinib · Positron emission tomography

Introduction

Aggressive fibromatosis (AF, also known as desmoid tumours) comprises a group of fibromatous proliferative diseases of similar microscopic presentation, which in their biological behaviour are classified between benign fibrous tissue proliferations and fibrosarcomas. AF typically occurs in the abdomen, but may also affect the extremities and trunk [1]. The incidence is less than 3% of soft tissue sarcomas [2]. AF is therefore a distinctly rare tumour and about three to four cases per 1 million of the US population are seen. Desmoids occur between the ages of 15 and 60 years, but particularly during early adolescence and with a peak age of about 30 years. There is a special relationship between desmoids and familial adenomatous polyposis (FAP, Gardner syndrome). An incidence of 3.5 to 32% has been reported in these patients [3, 4].

The first-line therapy for locally circumscribed AF is surgical resection. The growth pattern of these tumours is deep infiltrating, and there is no tumour capsule. Since the boundaries of the tumours are difficult to distinguish intraoperatively from scars and connective tissue, margin-negative (R0) resection is not always possible, and adjuvant radiotherapy is therefore common. AF, however, has a high local relapse rate after surgery and/or radiotherapy and exhibits locally aggressive growth. Although AF rarely forms metastases, it can often take a multiply relapsing,

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multifocal course, and therefore may not be amenable to curative surgical treatment. In this situation, pharmacotherapy is often used to prevent disease progression [5]. The primary aim is to preserve the patient's quality of life which is threatened by loss of function and pain caused by the proliferative disease. Therapeutic approaches to the treatment of recurrent and/or nonresectable AF comprise antihormonal therapy (e.g. tamoxifen), nonsteroidal antiinflammatory drugs (e.g. COX-2 inhibitors) and chemotherapy regimens, with highly variable results [6, 7]. It has not yet been possible to establish an optimal therapy protocol for this disease. A multidisciplinary approach comprising surgical intervention, radiotherapy and antiproliferative treatment is necessary [8].

Imatinib mesylate is a small-molecule selective inhibitor of the tyrosine kinases ABL, ABL-related gene product (ARG), KIT, and platelet-derived growth factor receptors α and β (PDGFRA and PDGFRB) [9, 10]. Dysregulation of imatinib-sensitive tyrosine kinases is a key factor in the pathogenesis of several malignancies, and imatinib treatment provides dramatic benefit in patients with such cancers [11]. Notably, imatinib is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia and metastatic gastrointestinal stromal tumours [12, 13], with the latter commonly having pathogenic mutations of the tyrosine kinases KIT (80–85%) or PDGFRA (5%) [14, 15].

Initial studies on the use of imatinib in AF showed a response in two patients with extraabdominal AF [16]. In contrast to other imatinib-responsive tumours, in AF it is uncertain whether or not the response is due to the inhibition of known imatinib targets such as KIT, ABL, ARG and PDGFRA/B kinases. In chronic myeloid leukaemia or gastrointestinal stromal tumours, specific genomic mutations and chromosomal translocations have been demonstrated. On the other hand, in AF no such genomic changes have been observed, showing that the response to imatinib is not attributable to c-kit expression [17]. Heinrich et al. treated 19 patients with AF with 800 mg imatinib daily [18]. Three patients showed partial response (PR) and four showed stable disease (SD). Genomic analyses revealed no mutations of KIT, PDGFRA or PDGFRB. Two further studies have shown promising results. In a study by Penel et al. in 40 patients with relapsing or refractory AF, a complete response was seen in 3% of patients, PR in 9% and SD in 83% [19]. Progression-free survival at 6 months was 74% and 69% at 12 months. These results were recently updated and showed a progression-free survival of 55% at 2 years [20]. Chugh et al. observed similar promising responses and nonprogression rates in 51 patients [21].

In soft-tissue sarcomas, imaging modalities such as CT and MRI can be used for the determination of tumour localization, size, and infiltration of the surrounding tissue

as well as the presence of satellite metastases. However, it has not been well established whether a significant change in tumour size is a meaningful indicator of patient outcome. Standard radiographic response has not correlated consistently with histological response, or disease-free or overall survival [22]. Other methods to identify patients who are likely to benefit from chemotherapy or other agents would be useful. Therefore, PET with ^{18}F -FDG has been increasingly used in oncology because it allows functional imaging of viable tumour tissue [23]. FDG PET can visualize soft-tissue sarcomas and detect local and distant recurrence of disease [24]. The standardized uptake value (SUV) correlates well with the metabolic rate of FDG accumulation in tumour cells [25]. Hence, the SUV could function as an easily measurable surrogate of tumour viability during therapy. In a group of 46 patients with localized, intermediate-/high-grade soft-tissue sarcoma of an extremity, it was demonstrated that changes of the SUV after neoadjuvant chemotherapy can be used to predict therapy outcome [26]. This study and other reports in the literature suggest that FDG PET can act as a noninvasive method to predict patients who are less likely to benefit from doxorubicin-based chemotherapy [27].

The purpose of the present pilot study, which to our knowledge is the first covering this topic, was to investigate semiquantitative FDG PET in AF patients undergoing treatment with imatinib.

Patients and methods

Patients

The pilot study included nine patients with AF. Their characteristics including gender, age, tumour site, and previous treatments are summarized in Table 1. All patients were referred to our outpatient service with the diagnosis of AF confirmed by histology obtained from surgical specimens. Tumour specimens were classified according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system [28]. The indication for inclusion was progressive disease, not amenable to surgical resection with R0 intent or accompanied by an unacceptable function loss or deficit. Patients were treated with imatinib at the Mannheim University Medical Center, University of Heidelberg, between May 2006 and March 2009. The research was carried out according to the principles set out in the Declaration of Helsinki of 1964 and all subsequent revisions.

Imatinib

Imatinib mesylate was supplied as 400 mg capsules to be taken orally (Novartis Deutschland, Nurnberg, Germany). All

Table 1 Patient characteristics (n=9)

Characteristic	Value
Gender (<i>n</i>)	
Female	6
Male	3
Age (years)	
Median	41.8
Range	19–67
Histology (<i>n</i>)	
Aggressive fibromatosis	9
Tumour site at initial diagnosis (<i>n</i>)	
Abdomen/trunk	7
Extremities	2
Previous treatment (<i>n</i>)	
None	3
Surgery alone	3
Surgery plus radiotherapy	3
Systemic treatment	1

patients with advanced and/or nonresectable disease started imatinib therapy at a daily dose of 400 mg, and the dose was escalated after 2 weeks to 800 mg daily (2×400 mg). Median duration of imatinib treatment was 7.9 months (range 4–19 months) until the time of data acquisition. In spite of CTCAE grade I/II fatigue and oedema, no major (grade III and IV) toxicities occurred.

Imaging studies

Patients were examined using FDG PET prior to starting and during imatinib treatment. The treatment/imaging algorithm was as follows: (a) an initial PET study was performed as baseline before the start of imatinib treatment; (b) a second PET study was performed for therapy monitoring after 1–3 months (if SUV showed a decrease or was stable imatinib treatment was continued); (c) another follow-up PET study was performed in some patients for further treatment monitoring. Conventional imaging of the same target lesion using CT and/or MRI was performed in parallel to determine the response according to the Response Evaluation Criteria in Solid Tumors (RECIST) and to localize target lesions. The results of this imaging served as reference to evaluate the response determined with FDG PET. Dynamic PET studies were performed after intravenous injection of 300–370 MBq FDG for 60 min. A dedicated PET system (ECAT EXACT HR plus, Siemens, Erlangen, Germany) was used for patient studies as described previously [29]. The last images (55–60 min after injection) were used for semiquantitative analysis.

PET cross sections were reconstructed with an image matrix of 256×256 using an iterative reconstruction

program. Images were corrected for scatter and attenuation. Volumes of interest (VOI) were placed over the lesion. To acquire information about tumour viability, the hyper-metabolic areas of the tumours were evaluated and hypo-metabolic areas that correlate with necrotic tissue were excluded. The SUVs in the tumours were calculated according to the following equation:

$$\text{SUV} = \text{tissue concentration (MBq/g)} / [\text{injected dose (MBq)} / \text{body weight (g)}]$$

The SUV reflected the average SUV value provided by the quantification software in a VOI. This value is more robust than the maximum SUV (SUV_{max}), because the average SUV is less influenced by the parameters used for image reconstruction and by potential artefacts, and SUV_{max} is highly dependent on the statistical quality of the images and the size of the maximal pixel [30]. The PET images were analysed by two nuclear medicine physicians together using the software package Pmod (Pmod Technologies, Zurich, Switzerland) [31].

Statistical analysis

Due to the small number of patients we performed a descriptive analysis of the data. Progression-free survival was defined as the time from the start date of imatinib therapy until tumour progression, end of therapy or data acquisition. Progression-free survival and SUV values are given as median and range.

Results

Clinical response based on RECIST

First, a CT and/or MRI scan was performed in all patients prior to the start of treatment with imatinib. Restaging was performed using CT and/or MRI every 3 months after the start of imatinib treatment. Remission status was evaluated according to RECIST based on tumour shrinkage as shown on the CT and/or MRI scan. Clinical outcomes according to RECIST were as follows: seven patients with SD, and two patients with PD. The median progression-free survival from the start date of therapy until the end of therapy or data collection for all patients was 9.1 months (range 4–19 months). Progression-free survival at 6 months was 67%. All patients were alive at the time of data acquisition.

Clinical response based on PET imaging

Initially, we evaluated 16 patients with AF using FDG PET. The median average SUV for all patients was 2.3 (range 0.6–4.2) and the median SUV_{max} was 4.1 (range 1.0–8.1). Of these 16 patients, 9 were actually treated with imatinib

Table 2 PET results in nine patients with AF treated with imatinib

Patient no.	Age (years)	Tumour location	Treatment duration (months)	Average SUV		SUV change (%)	Response according to RECIST	Progression-free survival (months)
				Initial	Follow-up			
1	61	Chest	6	2.9	2.5	-14	Progressive disease	6
2	67	Pelvis	5	3.2	3.4	6	Stable disease	5+
3	28	Retroperitoneal	4	4.2	3.3	-21	Stable disease	4+
4	42	Mesenterium	4	3.0	2.8	-7	Progressive disease	4
5	19	Chest	4	3.3	1.7	-48	Stable disease	15+
6	32	Supraclavicular	6	2.1	1.9	-10	Stable disease	6+
7	25	Upper limb	17	3.1	1.5	-52	Stable disease	17+
8	67	Gluteal muscle	19	2.8	1.3	-54	Stable disease	19+
9	35	Pelvis	6	2.8	1.7	-39	Stable disease	6+

+: patient still progression-free at the time of data collection.

and further evaluated using FDG PET (Table 2). Figure 1 shows the average SUV values from the sequential PET examinations in each patient. In four patients more than two PET examinations were performed during imatinib treatment, but for further statistical evaluations and comparison only the initial PET and the examination with the lowest SUV were chosen. In the nine analysed patients, the median average SUVs were 3.0 (range 2.1–4.2) before treatment and 2.2 (range 1.3–3.4) after treatment. The median SUV_{max} were 5.5 (range: 2.8–8.1) before treatment and 3.9 (range: 2.6–5.7) after treatment. Therefore, in the evaluated patients, the median average SUV decreased by 27% and the median SUV_{max} decreased by 29% between sequential PET examinations; no patient showed a substantial increase in SUV.

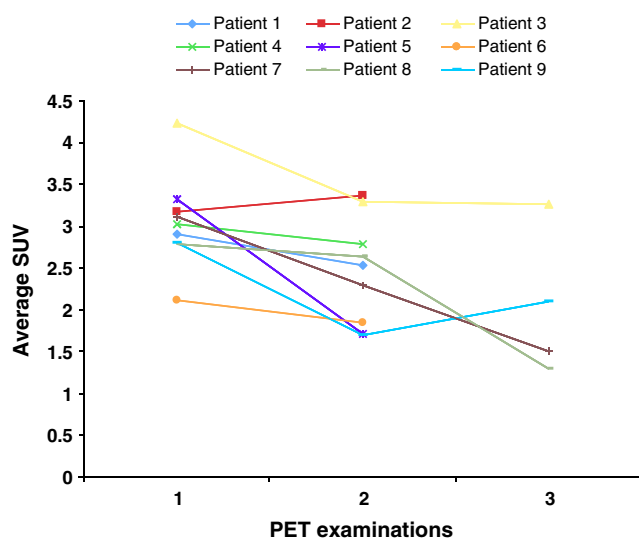


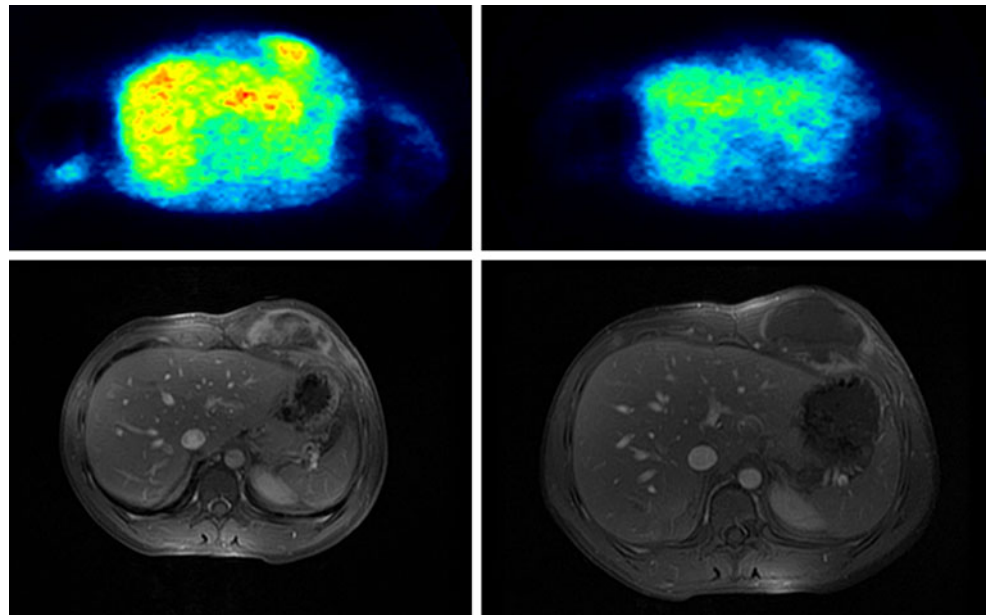
Fig. 1 Average SUVs from the PET examinations in each of nine patients

We compared the average SUVs with the clinical response data according to RECIST using conventional MRI and/or CT. The two patients with PD (patients 1 and 4) showed decreases in average SUVs of only 7% and 14% (13% and 15% for SUV_{max} , respectively). In contrast, patients with SD showed SUV decreases of up to 54% (58% for SUV_{max}). Two patients treated with imatinib for 17 and 19 months (patients 7 and 8) showed the highest SUV decreases of 52% and 54%, respectively. In the literature, for soft-tissue sarcomas a cut-off value of 40% reduction from baseline has been used to differentiate responders [32]. Among our patients, three showed a decrease in SUV of more than 40% (48%, 52% and 54%, respectively); however, response status according to RECIST was SD. Hence, three patients showed a significant decrease (>40%) in SUV between sequential PET examinations, whereas the other six patients showed stabilization or a decrease of <40% in SUV, however, only two of these patients showed disease progression according to RECIST. No patient in this series demonstrated a substantial increase in SUV.

Patient example

In order to demonstrate that PET imaging may provide additional information compared to conventional MRI and/or CT, we describe the case of one of our AF patients (Fig. 2). A 19-year-old man was diagnosed in 2007 with AF of the thoracic/abdominal wall (patient 5, Table 2) and was treated preoperatively with imatinib 800 mg daily. The FDG PET study before treatment with imatinib showed an average SUV of 3.3 and a SUV_{max} of 5.5 (Fig. 2, top left). After 4 months of treatment with imatinib, the FDG PET study demonstrated a decrease in the average SUV to 1.7 (48% decrease) and in the SUV_{max} to 3.1 (44% decrease) (Fig. 2, top right). The corresponding conventional MRI

Fig. 2 A 19-year-old man with AF of the thoracic/abdominal wall (patient 5, Table 2) diagnosed in 2007 was treated preoperatively with imatinib 800 mg daily. The FDG PET images before treatment (*top left*) and after 4 months of treatment (*top right*) show a decrease in FDG uptake (average SUV decreased from 3.3 to 1.7 and SUV_{max} from 5.5 to 3.1) (colour scales are directly comparable, 0–10 SUV). The corresponding conventional MR images documented SD according to RECIST (*bottom*)



scan documented SD according to RECIST (Fig. 2, bottom). The patient was treated by complete resection and was still progression-free 15 months after the start of imatinib treatment. This case underlines the common finding that the structure of the tumour may change reflected by a decrease in the average and the maximum SUV caused by a change in vessel density, blood circulation or necrosis, even though the tumour size itself remains stable.

Discussion

There have been different indications for the use of PET in soft-tissue sarcomas. It has been used to predict the malignant potential and grade of tumours, to stage malignant disease, to monitor tumour response to chemotherapy, to predict the clinical benefit from chemotherapy, and to detect tumour recurrence after primary therapy [33]. However, most studies have analysed only a small number of patients and have used different imaging protocols and evaluation procedures. Therefore, comparison of the different studies and analyses is difficult. Nevertheless, there is no doubt that FDG PET is useful in the clinical management of sarcoma patients [27].

During the last decade change in tumour size in response to cytotoxic treatment has been the parameter to predict the therapeutic benefit for the patient. However, changes in tumour size measured with CT and/or MRI do not correlate consistently with the outcome in sarcoma patients. Especially for gastrointestinal stromal tumours (GIST), this finding has been well documented. A study of FDG PET in imatinib-treated GIST showed that patients with normalization of tumour SUV within the first month of treatment

have a significantly longer time to disease progression and better overall survival than those patients with increased FDG accumulation [34]. FDG PET appears to be more useful than CT/MRI imaging in GIST to predict response to therapy. Moreover, there is doubt if RECIST even adequately describes the remission status following chemotherapy or therapy with other targeted agents. Therefore, in a recent issue of the *Journal of Nuclear Medicine*, a new classification of response criteria, the so-called “PERCIST” (positron emission tomography response criteria in solid tumours), was introduced. This system takes into consideration changes in both tumour volume and metabolism [35].

To our knowledge, the study reported here is the first series worldwide of AF patients undergoing imatinib treatment monitored using sequential PET imaging. The purpose of the study was to compare SUV values in patients with desmoids undergoing imatinib treatment and to identify those patients likely to benefit from treatment, with the intention to determine if or ensure that imatinib works. In our patient population, a significant decrease (>40%) in the SUV between sequential PET examinations was found in three patients in SD (33 %), whereas six patients showed stabilization or a decrease of <40% in the SUV. There was no patient in this series who showed a substantial increase in SUV. Considering the fact that patients had to demonstrate PD to enter the study, the high proportion of patients (78%) with SD indicates a significant benefit for the patients. Two patients treated for 17 and 19 months with imatinib demonstrated the highest SUV decreases of 52% and 54%, respectively, indicating that prolonged PET response may depend on the treatment duration with imatinib. RECIST is inadequate to describe responses seen in patients with desmoid tumours. Complete or even partial responses are seen in less than 10% of

patients being treated with imatinib [19–21]; most patients show disease stabilization or a minimal shrinkage of the tumour. However, considering the fact that patients were inoperable or demonstrated PD at the time of entering the study, control of symptoms and stabilization of the disease mean a substantial clinical benefit for most of the patients initially suffering from pain or functional loss.

PET examinations seemed to confirm the characteristics of imatinib therapy in AF patients. Imatinib has a remarkable ability to stabilize tumours and slow their growth as reflected by our results regarding SUVs. Of course, compared to high-grade soft-tissue sarcomas, baseline SUVs are relatively low in desmoid tumours (median average SUV of 3.0). Therefore, the SUV changes documented in those undergoing treatment with imatinib were relatively small. We were able to show that PET imaging of AF patients undergoing treatment with imatinib may be used to determine and/or monitor whether patients benefit from imatinib therapy or not. For most of the patients benefit means arrest of progression. PET imaging could be used to monitor imatinib treatment in patients with desmoid tumours in the absence of adequate CT and/or MRI imaging for these rare tumours [36].

Prediction of therapy response is a topic that raises several questions concerning the handling of data. Most studies monitoring chemotherapeutic effects using PET in oncological patients are based on simple quantification methods for data analysis, e.g. SUV or tumour-to-normal tissue ratio. However, the question is how reliable is baseline SUV or its change for therapy response assessment. Full dynamic quantitative studies provide the possibility to extend quantification and get data about FDG kinetics. In two recently published papers from our group, we discussed this issue and found that using dynamic PET, the best results for a group-based analysis of response or nonresponse are obtained with a multiparameter analysis including the mean absolute values of mean SUV and the baseline and the follow-up study [37, 38]. These dynamic PET studies provide more accurate data regarding prediction of response, but they are more time-consuming than routine clinical studies and are therefore more expensive.

Summary

FDG PET will certainly play an increasingly important prognostic and predictive role in the management of soft-tissue sarcomas. It could be used to assess the aggressiveness of a tumour in order to make clinical decisions as to whether treatment is useful for the patient or not. Our present data suggest that the effects of imatinib treatment in patients with desmoid tumours can be characterized by PET examinations. Imatinib shows a remarkable ability to stabilize tumours and slow their growth as indicated by SUV stabilization or a decrease in SUV of up to 54%. Furthermore, PET imaging

may be used to predict response to therapy early in the course of treatment with cytotoxic chemotherapy and targeted agents such as kinase inhibitors such as imatinib. However, more data need to be evaluated. PET imaging may complement radiological tomography and histological grading, and thus improve the assessment of AF patients, potentially influencing therapeutic decisions in the future.

Conflict of interest None.

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