**Abstract**

**Introduction**
Gastrointestinal stromal tumours (GISTs) represent a major fraction of gastrointestinal sarcomas, frequently showing c-kit exon 11 mutations and associated with a good response to imatinib mesylate. Secondary resistance to imatinib has also been reported during therapy; therefore, clinicians need non-invasive tools for early assessment of treatment response due to traditional morphologic criteria [X-rays and computerized tomography (CT)] being unsuccessful.

We report upon a patient with GIST with exon 11 mutation showing excellent response to imatinib mesylate, only a few days after initiation of the therapy and persisting for 18 months of follow-up. Here we also provide a short review of the recent literature on this topic.

**Conclusion**
There is evidence that F-FDG PET and PET/CT could be used to optimally monitor c-kit inhibitor therapy in GISTs, detecting early responders, non-responders and secondary resistance, thereby allowing better patient management.

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**18F-FDG PET/CT may detect early response to Imatinib mesylate in GISTs with exon 11 mutation: case report and critical review of literature**

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**Introduction**
Gastrointestinal stromal tumours (GISTs) are rare malignancies even though they represent the most relevant part of the gastrointestinal (GI) tract sarcomas. In most cases, GISTs are localized in the stomach and small intestine, followed by the colon and rectum. GISTs are derived from Cajal cells in myenteric plexus; they are frequently marked by the expression of the c-kit tyrosine kinase receptor. C-kit is a tyrosine kinase and is normally activated as a ligand by stem cell factor; a mutation of the c-kit proto-oncogene activates the tyrosine kinase in the absence of physiologic stimulation, thereby leading to unstrained cell proliferation.

The majority of GISTs (75%–80%) shows gain-of-function mutations of transmembrane receptor c-kit, which causes continuous activation of cell proliferation. The most common is the exon 11 mutation. Genetic mutation analysis allows investigation of the relationship between the mutations occurred and response to drugs, such as imatinib mesylate. Imatinib mesylate is a tyrosine kinase inhibitor of tumour growth, and it has been demonstrated to be effective in GIST treatment. It is currently the first-line drug in advanced GISTs.

Recent studies show that 85% patients with c-kit exon 11 mutation respond to imatinib mesylate; nevertheless, it has been reported that resistance to this drug may occur during therapy. This phenomenon needs to be disclosed as early as possible to change the therapeutic strategy, improve the clinical outcome and reduce the cost of ineffective therapies. In this regard, the response evaluation criteria in solid tumours (RECIST) criteria which relates to morphological examinations, mainly contrast-enhanced computed tomography (CT), are unsatisfactory in assessment of GISTs response because changes in tumour size may be minimal at an early post-therapy evaluation or the lesion could be even larger because of intra-tumoural necrosis or haemorrhage. There is recent evidence that a functional imaging modality such as 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) or a hybrid imaging modality such as PET/CT could achieve this goal.

This paper reports the case of a GIST patient treated with imatinib mesylate and showing an excellent response as documented by 18F-FDG PET/CT only a few days after initiation of the therapy and persisting for 18 months of follow-up. We also reviewed the relevant literature pertaining to the response monitoring tools in GISTs.

**Discussion**
In April 2008, a 54-year-old male patient underwent surgery for GIST T2N0M0 with mutation of exon 11. In August 2010, a controlled CT revealed bone and liver GIST metastasis that was proven at biopsy. Therapy with imatinib mesylate was scheduled. Before initiating therapy, the patient underwent baseline 18F-FDG PET/CT and repeated an early PET/CT examination 10 days after initiation of the therapy. Subsequent PET/CT controls during imatinib mesylate therapy...
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It is interesting to observe that in this case, 18F-FDG PET/CT was able to detect a good response at a very early stage after initiation of imatinib mesylate therapy and also demonstrated the efficacy of such therapy during follow-up. 18F-FDG PET/CT was performed with the patient in fasting condition after injecting 2.2 MBq/kg BW of 18F-FDG. Data acquisition started 60 min after the injection. We used a hybrid PET/CT scanner equipped with a 16-slice CT to acquire 3D-PET data (Discovery STE, General Electric, Milwaukee, WI, USA).

In the presented case, 18F-FDG PET/CT demonstrated a very early therapy response, 10 days after initiation of imatinib mesylate therapy. There are only a few similar case reports in literature, and all report similar results. Shinto et al.12 reported good metabolic response of a large abdominal GIST mass after 24 h of administration of a single dose of imatinib mesylate. Heinicke et al.13 and Jager et al.14 reported GIST cases with a strong decrease in FDG uptake after one week of imatinib therapy, matching with the overall treatment response and with a prediction sensitivity of 93%14. Gelibter et al.15 presented two GIST cases in which FDG PET demonstrated a complete absence of metabolic activity in known metastatic sites, confirming the clinical impression, despite of CT indicating a progressive disease.

With the advent of targeted therapies, oncologists need a reliable tool to identify the responders who will benefit from the treatment and non-responders who need a change in therapeutic management16. For this reason, there is a growing interest in literature about the limitations of the currently used monitoring morphologic techniques (typically contrast-enhanced CT) and the research of response criteria different from RECIST.

A frequent feature of GISTs during therapy is the change in density at CT, especially in the liver: some lesions were performed every 6 months; the last one was performed in May 2012. Figures 1–3 show metastatic localizations in both baseline conditions, 10 days after initiation of the therapy and during prolonged follow-up.

Figure 1: (a) Baseline 18F-FDG PET/CT before imatinib mesylate treatment: CT (left) and 18F-FDG PET (right) transaxial images showing bone lesion on the fifth thoracic vertebra; (b) 18F-PET/CT examination after 10 days of therapy: 18F-FDG PET (right) transaxial images showed complete metabolic response, while the CT scan showed no significant variations (left); (c) 18F-PET/CT examination after 18 months of therapy: 18F-FDG PET (right) transaxial images confirmed the complete response, while CT scan showed a little shrinkage of the lesion only in the 18-month control (left).
may become more hypodense after therapy, and several isodense localized lesions may become more cystic and consequently more visible, thus resulting in a CT progression according to size/number criteria\(^1\), such as RECIST. However, morphological changes may occur from weeks to months; the mean time to objective tumour shrinkage at CT scan is to be approximately 13 weeks\(^1\).

For these reasons, the authors agree that RECIST morphologic criteria seem to be over reached by alternative methods, which include new CT criteria and FDG PET or PET/CT evaluation.

There is a growing agreement in literature that FDG PET is a powerful tool in monitoring the response outcome in GISTs treated with imatinib mesylate and its main role in the evaluation of early response to therapy.

Choi and colleagues\(^1\) found that size-based criteria significantly underestimated the response to imatinib mesylate, while evaluation on the basis of changes in tumour nodules, density, vascularization, metabolic behaviour as well as changes in size could be more accurate in predicting response to therapy and prognosis. These data indicate that a combination of the values of tumour size and density on CT may predict the time-to-progression (TTP) as well as the maximum standardized uptake value (SUV\(\text{max}\)) in FDG PET, which was also confirmed in some recent studies by the same group\(^8\).

Holdsworth’s results indicated that the EORTC criteria for FDG PET were predictive of outcome, while changes in CT bi-dimensional measurement after 1 month of treatment did not correlate with the patients’ outcome\(^1\). Similarly, in a pivotal trial, Van den Abbeele et al. agreed with the EORTC criteria and found that patients reaching an SUV\(\text{max} \leq 2.5\) after 1 month of treatment fared better than those who did not; moreover, in their following study aiming at optimizing response criteria, they also showed that an absolute value of SUV\(\text{max}\) of 3.4 and a 40% reduction in SUV\(\text{max}\) after 1 month were even more predictive of time-to-treatment-failure (TTF) in comparison with EORTC assessment\(^1\).

The long-term outcome of imatinib mesylate treatment monitored with FDG PET, contrast-enhanced CT and in-line FDG PET/CT has been investigated;

**Figure 2:** (a) Baseline \(^{18}\)F-FDG PET/CT before imatinib mesylate treatment: CT (left) and \(^{18}\)F-FDG PET (right) transaxial images showing a left iliac bone lesion; (b) \(^{18}\)F-PET/CT examination after 10 days of therapy: \(^{18}\)F-FDG PET (right) transaxial images showed complete metabolic response, while the CT scan showed no significant variations (left); (c) \(^{18}\)F-PET/CT examination after 18 months of therapy: \(^{18}\)F-FDG PET (right) transaxial images confirmed the complete response, while the CT scan showed no significant variations (left).
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in this study, a post-treatment complete response at PET was predictive of significantly better overall survival (OS) and longer TTP, while CT results were not suitable for OS and TTP\textsuperscript{18}. Moreover, Gayed et al. reported that in 54 patients treated with imatinib, FDG PET was a better ‘guide’ in therapy monitoring as it predicted response to the therapy earlier than CT in 22.5\% patients during follow-up, whereas CT predicted lack of response to therapy earlier than FDG PET in 4.1\%\textsuperscript{19}. Park et al. found a significant correlation between the Ki-67 index and SUV\textsubscript{max} ($p < 0.001$), reasonably expecting that higher SUV values occur in highly proliferating GISTs, thus allowing the prediction of malignant potential\textsuperscript{20}.

Another emerging issue is the role of FDG PET in identifying GIST patients’ refractory to imatinib mesylate who may benefit from other chemotherapies. In fact, PET may pick out patients with primary imatinib mesylate resistance, showing no or poor reduction in SUV\textsubscript{max} during imatinib treatment and even ‘flare phenomenon’ (intense glycolytic activity when imatinib is stopped prior to starting other drug therapies), but it can also aid in detecting secondary resistance caused by clonal de-differentiation. Further, Van den Abbeele et al. reported on re-emerging FDG uptake months/years after the end of imatinib therapy within the site of disease\textsuperscript{10}.

Prior et al. studied a population of GIST patients treated with sunitinib after imatinib failure and observed that FDG-PET may allow response assessment immediately after the first course of therapy. In fact, early metabolic response was strongly and independently predictive of progression-free survival (PFS) and OS, whereas various c-kit mutations and other clinical and histopathological factors were not correlated with PFS\textsuperscript{21}.

Finally, some authors agree that in-line PET/CT could be more useful than side-by-side PET and CT alone, because it maximizes the benefit and complementarity of each system\textsuperscript{10} and at the same time provides treatment response assessment and morphological information needed for planning surgical interventions\textsuperscript{8,18}.

Conclusion

This report adds new data to the recent literature, supporting the growing

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biogenetic mutations analysis. Therapy could be a good surrogate of initiation of imatinib mesylate performed within 2 weeks after secondary resistance to imatinib, thereby detection of not only early responders to imatinib therapy in GISTs. It allows the imaging modality to monitor c-kit inhibitors in patients with gastrointestinal stromal tumours. It may be an optimal non-invasive imaging modality to monitor c-kit inhibitors in patients with gastrointestinal stromal tumours. F-FDG PET/CT may be an optimal non-invasive imaging modality to monitor c-kit inhibitors in patients with gastrointestinal stromal tumours. F-FDG PET/CT may detect early response to Imatinib mesylate in GISTs with exon 11 mutation: case report and critical review of literature. OA Molecular Oncology 2013 Feb 01;1(1):1.

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References