ORIGINAL PAPERS

Patterns of extension of gastrointestinal stromal tumors (GIST) treated with imatinib (Gleevec)[®] by ¹⁸F-FDG PET/CT

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ABSTRACT

Background and aim: currently it is recognized the usefulness of ¹⁸F-FDG PET in assessing response to therapy with imatinib (Gleevec[®]) in the gastrointestinal tract sarcomas (GIST). To facilitate the follow-up of these studies is important to know the patterns of metastatic spread. The aim of this paper is to describe patterns observed in the ¹⁸F-FDG PET/CT.

Method: retrospective study included 29 patients who underwent ¹⁸F-FDG PET/CT after being diagnosed with unresectable or metastatic GIST. In total, 87 PET/CT studies were performed (1-6 controls per patient) with a mean time of follow-up 6-36 months. We analyzed the location of the lesions evidenced in PET, CT and fusion. Images were evaluated visually and semiquantitatively (SUV). In cases in which has been considered necessary, additional images have been undertaken: PET delayed imaging, intravenous contrast CT and inspiratory chest CT.

Results: the most common primary site was the stomach (41%), small bowel (35%), and rectum (24%). Significant changes in the location of metastatic disease between pre-treatment and the monitoring were observed, with the appearance of more extra-abdominal disease.

Conclusions: individualization of protocol studies and interpretation of PET, CT and fused images were required for evaluation of treatment response to imatinib. Hybrid ¹⁸F-FDG PET/CT provides an accurate determination of the extent of GIST. While the most common metastatic site is the liver and peritoneum, in the following cases are common extra-abdominal disease.

Key words: GIST. ¹⁸F-FDG PET/CT. Metastases.

Valls-Ferrusola E, García-Garzón JR, Ponce-López A, Soler-Peter M, Fuertes-Cabero S, Moragas-Solanes M, Riera-Gil E, Carrió-Gasset I, Lomeña-Caballero F. Patterns of extension of gastrointestinal stromal tumors (GIST) treated with imatinib (Gleevec[®]) by ¹⁸F-FDG PET/CT. *Rev Esp Enferm Dig* 2012;104:360-366.

INTRODUCTION

GIST are gastrointestinal stromal tumors, account for 6% of all sarcomas and 3% of gastrointestinal tract tumors, described incidence of 1-2 cases/100,000 population (1). Over 90% of cases occur in patients older than 40 years, with a slight predominance in men (2).

GIST were originally classified as leiomyomas, leiomyosarcomas and leiomyosarcomas, characterized by expression of a mutated membrane receptor tyrosine kinase activity (CD117 or C-KIT) in 90% of cases. Additionally, 60-70% of cases also express CD34 (transmembrane glycoprotein). These characteristic allows specific treatment with drugs that inhibit signal transduction mediated by KIT, inhibiting proliferation and promoting apoptosis of tumor. Imatinib (Gleevec[®]) is the drug used in clinical practice to treat cases in which the primary lesion is unresectable or when there metastatic lesions (1,3). Ten percent of cases do not express the membrane receptor CD117 (1).

About 30% of patients were asymptomatic and diagnosed was made for an incidental radiological finding or at the time of autopsy. Clinical manifestations are related to the location and tumor size, the most frequent abdominal pain, intestinal bleeding, anemia, weight loss, nausea and vomiting (2,4). The most frequent primary tumor location is the stomach, 50-60% of patients, followed by the small bowel, with 25-35% (2). The colon, rectum and esophagus are less frequent locations (5).

At the time of primary tumor diagnosis, 15-27% of the cases have already metastasized. Over 50% of high risk GIST present with recurrence or metastases within a period

Received: 17-01-2012

Accepted: 10-04-2012

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of 10 years. It has come to describe disease progression at 30 years of primary tumor diagnosis (3,6,7). GIST malignant forms represent 20-30% of total, (4) many of them incurable with a median survival after diagnosis of about 12-19 months (3).

The most common metastatic site is the liver (65%), followed by the peritoneum (50%), with 20% of patients with metastases in both locations. While extra-abdominal locations are considered very rare (< 10%) (6,8). Many studies have shown a significant increase in survival in patients with metastatic or recurrent GIST treated with imatinib. In addition, you can change the dose of treatment and even have appeared others treatments derived from tyrosine kinase as sorafenib, so it is very important, proper monitoring of these patients.

The degree of uptake of ^{18}F -fluorodeoxyglucose (^{18}F -FDG) in GIST is usually intense. This described a correlation between histological grade of malignancy and ^{18}F -FDG avidity by GIST, which seems to reflect the metabolic mitotic activity, so that PET may be a direct measure of tumor aggressiveness and thus of prognosis (3,9,10).

The main utility of ^{18}F -FDG PET/CT in GIST patients is to monitor response to treatment with imatinib. Metabolic changes in response to Imatinib may be manifested at 24 hours after administration of a single dose, so PET scan predicts therapeutic response to imatinib earlier as morphological CT changes (3,11).

However, to establish treatment response is essential to know the metastatic spread in GIST patients. Therefore, the aim our observational study is to describe these patterns of metastatic spread.

MATERIALS AND METHODS

Retrospective study including 29 patients, 10 women and 19 men, mean age 60 ± 12 years, who were attended in the last 4 years, for a ^{18}F -FDG PET/CT study after have been diagnosed with unresectable GIST or metastatic disease. None had started treatment with Imatinib. All were scanned again with PET/CT to assess the efficacy of treatment. In total, 87 studies were evaluated ^{18}F -FDG PET/CT (between 1-6 controls per patient) with a mean follow-up of 6 to 36 months.

PET/CT studies were performed at 60 ± 10 minutes after injection of 370 ± 185 MBq of ^{18}F -FDG in a PET/CT scanner Gemini (Philips) equipped with GSO crystals and 16 helical CT. Reconstructed images were done using full 3D reconstruction.

PET/CT included whole body, from the base of the skull to the upper third of the lower limbs. Additionally, delayed PET images were acquired, intravenous contrast CT and inspiratory chest CT. The assessment of all PET/CT studies was performed visually and semiquantitatively (SUVmax)

Fig. 1. Coronal PET, axial fusion ^{18}F -FDG PET/CT and liver CT images. Patient with history of gastric GIST and liver M1 resected. Suspected persistent disease vs. hepatic cysts in CT. Whole body PET/CT performed one hour after administration of 7.4 mCi of ^{18}F -FDG showed two pathological deposits adjacent to bowel loops, one of them in right subdiaphragmatic region (SUVmax 5.7 and 3.6) related with peritoneal tumor implants.

independently by two nuclear medicine and a specialist in radiology.

For each patient, we analyzed, in each of the controls, all new abnormal deposits of ^{18}F -FDG. In addition, we recorded changes of activity in each of these images, but without establishing criteria for treatment response, since it is not the aim of our study.

Lesions that involved a change of staging have been characterized by cytology and/or histology.

RESULTS

- *Primary tumor*: the most common primary site was the stomach (12-41% of cases) followed closely by the small bowel (10-35%), and a lower percentage of patients, rectal location (7-24%).
- *Pre-treatment study*: twenty-six of the 29 patients in pre-treatment PET/CT showed lesions suspicious for metastasis. Of these, in 21 patients, the disease was intra-abdominal, while only in 5 patients disease was detected intra- and extra-abdominal sites. In none, extra-abdominal disease location alone was observed.

The most metastatic common intra-abdominal site was: liver (19 patients), followed by peritoneal implants (12 patients), infra-diaphragmatic lymph-nodes (1 patient). The extra-abdominal locations were infrequent (2 micro lung nodules, 2 pleural implants, 2 supra-diaphragmatic lymph-nodes, 1 soft tissue implant).

- *PET/CT follow-up*: in the various post-treatment controls, 10 of the 26 patients showed new lesions suspicious of metastasis. Of these, in four patients, the disease was intra-abdominal, in three intra- and extra-abdominal and in three patients extra-abdominal, exclusively.

In spite of pre-treatment studies, in follow-up PET/CT, extra-abdominal metastatic site was more frequent (2 lung lesions, 2 pleural implants, 2 bone lesions, 2 subcutaneous lesions, 1 supra-diaphragmatic lymph-node) that intra-abdominal, while the peritoneal is the single most frequent (5 patients), liver (2 patients), infra-diaphragmatic lymphonode (1 patient).

In both, pre-treatment and follow-up studies, SUV showed the highest values in liver metastases and peritoneal implants, with a large variability in all metastatic sites.

Fig. 2. Whole body, axial fusion ^{18}F -FDG PET/CT and chest CT. Patient with GIST of the small bowel, partial hepatectomy for metastases and subsequent treatment with Gleevec®, was admitted to our hospital for suspected sonographic progression. Whole body PET/CT performed one hour after administration of 8 mCi of ^{18}F -FDG showed multiple active images in the liver consistent with metastatic progression (the largest one SUVmax 6.2). Many of the abdominal-pelvic nodular images show intense uptake of ^{18}F -FDG related with peritoneal implants/lymph-node involvement (most notably in the left anterior pararenal space with a SUVmax 6.3). Also, detected a small hypermetabolic extra-abdominal focus in antero-superior left thoracic wall, which could be localized in the left internal mammary (SUVmax 1.8). At 4 months, she underwent a PET/CT scan, showing extra and intra-abdominal progression, confirming the origin of the lymph-node in the left internal mammary (SUVmax 3.3).

Table I and II collected location data of primary GIST, metastatic lesions, pre-treatment and follow-up false positives, indicating the SUV of all deposits of ^{18}F -FDG assessed.

- *Limitations:* in six patients, the abnormal deposits of ^{18}F -FDG being false positives: three in oropharyngeal cavity, one esophagitis, one soft tissue process and one inflammation in the lung. In four of these, the study also detected other lesions, finally diagnosed as metastases.

Infracentimetric lung lesions by CT in three patients were the only metastatic lesions showing no uptake of ^{18}F -FDG.

DISCUSSION

In patients with GIST, not suitable for surgical approach, treated with imatinib, literature describes intra-abdominal location as the most common, highlighting liver involvement (2,4). Our results in pre-treatment studies confirm that the most common site is the liver, on many occasions associated with peritoneal involvement. Also shows that are uncommon extra-abdominal metastatic sites.

Imatinib treatment response in patients with GIST is widely studied by PET (3,7) reason that was not included

in our study. However, in our series, we diagnosed new hypermetabolic lesions in 10 patients (38.5%) related with the aggressiveness of the disease.

This observational study shows significant changes in the location of metastatic disease between pre-treatment and follow-up studies. In follow-up studies more extra-abdominal disease appears. Thus, in seven patients new disease were located intra-abdominal (3 associated with additional involvement), 6 extra-abdominal metastases (and more importantly, in 3 of these, without intra-abdominal M1). This is the crucial teaching point of our series.

For correct re-staging in monitoring these patients, ^{18}F -FDG PET/CT has several technological advantages over other diagnostic tests. First, high affinity of ^{18}F -FDG in GIST patients permit to detect small lesions. Secondly, as a whole body technique allows the diagnoses of disease in remote locations, rare described. Furthermore, the use of integrated PET/CT scanners results in a correct anatomical localization of the hypermetabolic foci, substantially reducing false positives. If required, the procedure of PET/CT can be completed with a CT with intravenous contrast or thoracic inspiration.

Thus, PET/CT, in these patients, allows for maximum diagnostic capabilities, especially considering the follow-up when metastatic lesions appear most often in unusual locations, especially at extra-abdominal site.

Fig. 3. Coronal PET, axial fusion ^{18}F -FDG PET/CT and chest CT. Patient with history of gastric GIST presenting a nodular lesion in the left lung, new onset, a CT scan. Whole body PET/CT performed one hour after administration of 8 mCi of ^{18}F -FDG shows a small focal uptake of ^{18}F -FDG (SUVmax 1.4) corresponding with a CT nodule in the left upper lung lobe.

Table I. Location of primary GIST, metastatic lesions of pre-treatment, and false positive

<i>Tumor primario</i>	<i>Basal</i>	<i>1st control</i>	<i>2nd control</i>	<i>3rd control</i>	<i>4th control</i>	<i>5th control</i>	<i>6th control</i>
Stomach	FP (bucal) (4,5)	0					
Stomach	FP (lung) (3,5)	0					
Small bowel	Peritoneum (3,8)	↓	≈	≈			
Rectum	Peritoneum (7,8) FP (supra) (5,9)	↓					
Stomach	Liver (3,4)	0	0	0	0	0	0
Small bowel	Liver (4,2)	0					
Stomach	Liver (3)	0					
Small bowel	Liver (3,3)	0					
Small bowel	Liver (8,8)	0					
Small bowel	Liver (2,3) Peritoneum (2,5)	0 0					
Stomach	Liver (10,4) Peritoneum (4,5)	↓ 0					
Rectum	Liver (8,4) Peritoneum (3)	↑ 0					
Small bowel	Liver (3,5) Peritoneum (20,9)	0 ≈					
Stomach	Liver (1,9) Peritoneum (11,3) Pleura (1,5) FP soft tissue (4)	0 ↓ 0	0 ↓ 0	0 ↓ 0			
Stomach	Liver (19,8) Peritoneum (13,5) Supra (15,2) Soft tissue (8,9) Lung (0,6)	↑ ↑ ↑ ↑ ↑					
Stomach	Peritoneum (7,9) Pleura (6)	↑ ↓					
Stomach	0	0	0	0			

However, as reflected in our study, there have been false positives, so that all hypermetabolic foci, especially at infrequent location, must be corroborated by cytology or histology (FNA/BAG).

Treatment response to imatinib is the established indication of ¹⁸F-FDG PET/CT in GIST patients. Our study, observational and retrospective, suggests that the location of metastatic progression in patients during treatment with Imatinib is different for each developmental stage.

It is probably necessary to conduct a prospective longitudinal study, where in addition to assessing metabolic response to therapy, can replicate the process of metastatic spread as observed in our series.

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Table II. Location of primary GIST and metastatic lesions and false positives that occurred during the monitoring

Primary tumor	Basal	1 st control	2 nd control	3 rd control	4 th control	5 th control	6 th control
Rectum	Infra (10,9) 0	0 Lung (8,6)					
Small bowel	Liver (4,9) Lung (0,9) 0 0	≈ ≈ 0 0	≈ ≈ 0 0	↑ ↑ Pleura (3,5) 0	↓ ≈ ↓ 0	≈ ↑ ↑ 0	↑ ↑ ↑ Soft tissue (7,3)
Rectum	Liver (4) 0 0 0	0 0 0 0	0 Bone (3,4) 0 0	0 ↑ Peritoneum (5) Soft tissue (4,5)			
Small bowel	Liver (8,4) 0 0 0	↑ 0 0 0	↑ Peritoneum (9,1) 0 0	↓ ↓ 0 0	↑ ↑ Supra (3,3) Bone (6)		
Small bowel	Liver (4,1)	0	0	Liver (6,8)	≈	↓	
Stomach	Liver (10,4) 0 0 0	0 0 0 0	0 Liver (4,9) Peritoneum (3,5) Pleura (7,5)				
Small bowel	Liver (8,7) 0	↑ 0	↑ FP (bucal) (8,8)	↑			
Stomach	Liver (5,6) 0	0 Peritoneum (5,7)					
Rectum	Liver (6) 0	0 FP (bucal) (5)					
Rectum	Peritoneum (4,7) 0	↑ 0	↑ Lung (0,7)				
Rectum	Peritoneum (6,7) 0	0 0	0 Peritoneum (8)	0 ↑			
Stomach	Peritoneum (3,9) Supra (3) 0	↑ 0 Infra					

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