Improving diagnosis and treatment of gastrointestinal stromal tumor (GIST) patients: Results from the Dutch GIST Registry

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Paragraph 4.2

Early response evaluations by ^{18}F-FDG-PET/CT do not influence the management of patients with metastatic gastrointestinal stromal tumors (GIST) treated with palliative intent

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Abstract

Objective

The aim of this study was to investigate the impact of ^{18}F-FDG-PET/CT on treatment decision making in metastatic gastrointestinal stromal tumor (GIST) patients.

Methods

This study retrospectively evaluated ^{18}F-FDG-PET/CT scans to monitor response of metastatic GIST patients treated with palliative intent. Data from the Dutch GIST Registry was used. Early scans (<10 weeks after start of treatment) and late scans (>10 weeks after start of treatment) were scored on the impact in change of treatment.

Results

Sixty-one PET/CT scans were performed for treatment evaluation in 39 patients with metastatic GIST of which 36 were early scans and 25 were late scans. Early PET/CT scans led to a change in management in 5.6% of patients and late PET/CT scans led to a change in management in 56% of patients.

Conclusion

In patients with metastatic GIST, early response evaluation using ^{18}F-FDG-PET/CT is not recommended.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. GIST mainly occurs in elderly patients of both sexes and has an estimated incidence of 1-2 per 100.000 per year.(1) Metastatic or unresectable disease is described in 10 to 30% of patients with GIST.(2)

In metastatic GIST, systemic treatment with imatinib is the primary choice of treatment. Imatinib is a tyrosine kinase inhibitor that targets Bcr-ABL, c-KIT and PDGFRA. Since the introduction of imatinib, the survival of patients with GIST has improved significantly. The median overall survival of patients with advanced disease improved from 18 months to 5-6 years.(3-5) Treatment with imatinib leads to disease control in 70-85% of patients with advanced GIST with activating mutations in *KIT* exon 11, which is the most frequent site of mutation.(3) Treatment response monitoring is often performed using size and density measurements on CT scan.(6,7) Previous studies have shown that metabolic response measured by ^{18}F-FDG-PET/CT could predict imatinib responses within 1-8 days.(6-9) In patients treated with neo-adjuvant intent, ^{18}F-FDG-PET/CT has shown to change treatment in over half of patients.(10) Up until today no studies have been conducted assessing the influence of early response evaluation using ^{18}F-FDG-PET/CT in metastatic GIST patients. The aim of this study was to investigate the impact of ^{18}F-FDG-PET/CT on treatment decisions in GIST patients treated with palliative intent.

Methods

All GIST patients treated with palliative intent who were entered in the Dutch GIST Registry (DGR) and underwent an ^{18}F-FDG-PET/CT were included in this study. The DGR includes data of all GIST patients diagnosed since January 2009 in the 5 GIST centers in the Netherlands. These centers include the Netherlands Cancer Institute – Antoni van Leeuwenhoek, Erasmus University Medical Center, Leiden University Medical Center, University Medical Center Groningen and Radboud University Medical Center Nijmegen. Data acquisition was approved by the local independent ethics committees and was conducted in accordance with the Declaration of Helsinki. Data cut-off date was September 2017.

Patient and tumor characteristics were derived from the DGR. Baseline and response ^{18}F-FDG-PET/CT scans of metastatic GIST patients were evaluated and change in treatment was determined by assessing patients' medical records. Metabolic responders were defined as all patients with partial or complete metabolic response on ^{18}F-FDG-PET/CT, non-responders were defined as all patients with no response.

Change in treatment was defined as a switch in treatment strategy directly influenced by ^{18}F-FDG-PET/CT results and was divided in two categories: 1) change in surgical

treatment (e.g. surgery cancelled or change in surgical approach); 2) change in systemic treatment (change in dose, switch or stop systemic treatment).

The treatment evaluation scans were divided in two categories: early response scans and late response scans, with a cut off of 10 weeks after start of treatment. This cut off was based on the fact that response monitoring by CT in the majority of cases is performed approximately 10 weeks after start of treatment.

Two investigators (SF, MH) independently determined whether the reports of the ^{18}F-FDG-PET performed for response monitoring led to a change in management. Discrepancies were solved by consensus.

Statistical analyses were performed using IBM SPSS Statistics. Associations between change in management, the timing and results of ^{18}F-FDG-PET/CT and demographic and biological characteristics were assessed using Chi-square analyses for categorical variables and Mann-Whitney U for continuous variables. Kaplan Meier Estimates for Progression Free Survival were generated, stratified on metabolic responders and non-responders. Progression free survival was calculated from the date of start of systemic treatment until the date of progression, defined as the date on which treatment stopped due to disease progression. A p-value of <0.05 was considered statistically significant.

Results

In total, 888 GIST patients were entered in the DGR-database. Two hundred and twenty-one patients had metastatic disease. In total 105 ^{18}F-FDG-PET/CT scans were performed in 60 metastatic GIST patients. Eventually, 61 ^{18}F-FDG-PET/CTs were performed for response evaluation in 39 patients. (Figure 1) Patient characteristics of all 39 patients are described in Table 1.

Table 1: Patient Characteristics.

Characteristic	**Patients (*n*= 39)**
Sex	
Male	24 (61.5%)
Female	15 (38.4%)
Age in years (median; range)	69 (33-85)
Location primary tumor	
Gastric	21 (53.8%)
Small bowel	12 (30.8%)
Duodenal	2 (5.1%)
Colon	2 (5.1%)
Other	2 (5.1%)
Mutation status	
KIT exon 11	29 (74.4%)
KIT exon 9	2 (5.1%)
KIT exon 13	1 (2.6%)
KIT exon 17	1 (2.6%)
PDGRFA exon 18	1 (2.6%)
PDGRFA exon 12	1 (2.6%)
Unknown	4 (10.2%)
Secondary mutations	
Not reported/undetected	36 (92.3%)
Present	3 (7.7%)
Baseline Comorbidity - Charlson index score	
<4	33 (84.6%)
≥4	5 (12.8%)
Unknown	1 (2.6%)
Baseline PET available?	
Yes, FDG-avid	37 (94.9%)
Yes, but not FDG-avid	0 (0.0%)
No baseline available	2 (5.1%)

Patients received first line imatinib treatment in 52 out of 61 response evaluation scans (85.2%), second line sunitinib treatment in 6 scans (9.8%) and third line treatment (once with regorafenib and twice with nilotinib) in 3 scans (4.9%). In 36 out of 61 response scans (59%) a metabolic response was detected.

In total, 16 out of 61 (26%) ^{18}F-FDG-PET/CT scans led to change in management. Eleven out of 16 ^{18}F-FDG-PET/CT scans were performed directly after the diagnostic CT in order to clarify the indeterminate results of the CT. This involved a metabolic evaluation of possible progression seen on CT. The other five ^{18}F-FDG-PET/CT scans were performed to assess whether metabolic progression is seen in one or more lesions prior to surgery or switch in systemic treatment.

Thirty-six early response PET scans were performed with a median of 24 days after start of or change in systemic treatment (range 3-70, SD 18.7). 25 late response PET scans were performed with a median of 293 days after start of or change in systemic treatment (range 80-1212, SD 332). Metabolic response was detected in 28 early response scans (80%) and in 8 late response scans (33.3%).(Table 2)

Table 2: ^{18}F-FDG-PET/CT outcomes in 39 patients with response evaluation.

^{18}F-FDG-PET/CT outcomes	**Total n=61**	**Early response evaluation (n=36)**	**Late response evaluation (n=25)**
Metabolic response?			
Yes, complete response	16 (26.2%)	14 (38.9%)	2 (8%)
Yes, partial response	20 (32.8%)	14 (38.9%)	6 (24%)
No response	23 (37.7%)	7 (19.4%)	16 (64%)
No baseline available	2 (3.3%)	1 (2.8%)	1 (4%)
Response PET resulting in any change of management?			
Yes	16 (26.2%)	2 (5.6%)	14 (56%)
No	45 (73.8%)	34 (94.4%)	11 (44%)
Response PET resulting in a change in surgical treatment?			
Yes	10 (16.4%)	1 (2.8%)	9 (36%)
No	51 (83.6%)	35 (97.2%)	16 (64%)
Response PET resulting in a change in systemic treatment?			
Yes	6 (9.8%)	1 (2.8%)	5 (20%)
No	55 (90.2%)	35 (97.2%)	20 (80%)
Systemic treatment			
First line treatment	52 (85.2%)	32 (88.9%)	20 (80%)
Second line treatment	6 (9.8%)	2 (5.6%)	4 (16%)
Third line treatment	3 (4.9%)	2 (5.6%)	1 (4%)
Response PET performed after start of treatment (days)			
Median (range)	57 (3-1123)	24 (3-70)	293 (80-1212)

Out of 36 early response ^{18}F-FDG-PET/CTs (Figure 2), two scans led to a change in management (5.6%), while 14 out of 25 (56%) late response ^{18}F-FDG-PET/CTs led to a change in management. Late response ^{18}F-FDG-PET/CTs and lack of metabolic response were strongly correlated with change in management ($p < 0.001$ and $p=0.002$ respectively). One early scan led to a change in surgical management, concerning a cancellation of planned surgery due to unexpected progression in multiple lesions. The other ^{18}F-FDG-PET/CT scan led to a change in systemic treatment (switch from imatinib to sunitinib). Nine late ^{18}F-FDG-PET/CT scans led to a change in surgical management. In these 9 scans progression of a solitary metastasis was observed, which led to metastasectomy. The results of 5 late scans led to a change in systemic management, three of these scans led to an increase in dose and two scans led to a switch to sunitinib (Figure 3).

Survival analyses showed no significant difference in progression-free survival between responders and non-responders, with median PFS of 273 weeks (95% confidence interval (95% CI) 237-308 weeks) and 260 weeks (95% CI 135-384 weeks) respectively ($p=0.779$).

Discussion

In this study, we investigated the influence of ^{18}F-FDG-PET/CT on treatment strategies in patients with metastatic GIST. This is to our best knowledge the first study to assess the actual impact of this imaging technique on treatment decisions in metastatic GIST. Prior studies have suggested that early response evaluation using ^{18}F-FDG-PET/CT might have a significant impact on treatment changes in metastatic GIST.(10-16) One study has found a significant impact of ^{18}F-FDG-PET/CT in the management of neoadjuvant treated GIST patients.(10) In our current restrospective analysis in metastatic GIST, almost 95% of early response scans have not led to a change in management, whereas the late response scans led to a change in management in over half of the scans (56%).

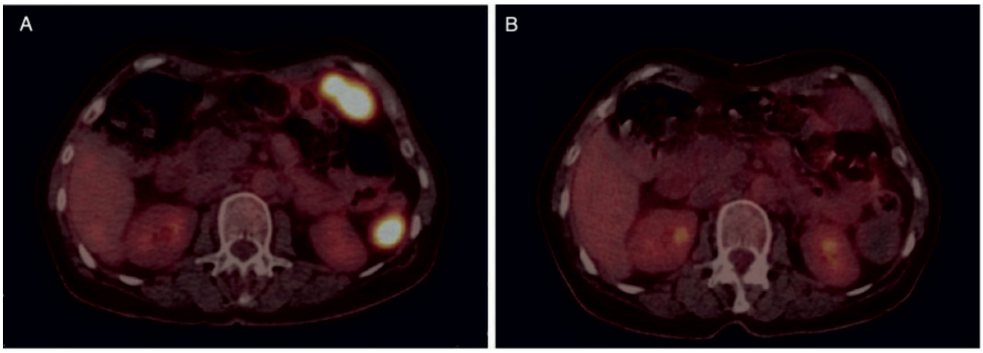

Figure 2: (A) Baseline ^{18}F-FDG-PET/CT of a GIST patient with a KIT exon 11 mutation. (B) Complete metabolic response 2 weeks after start of imatinib 400 mg daily.

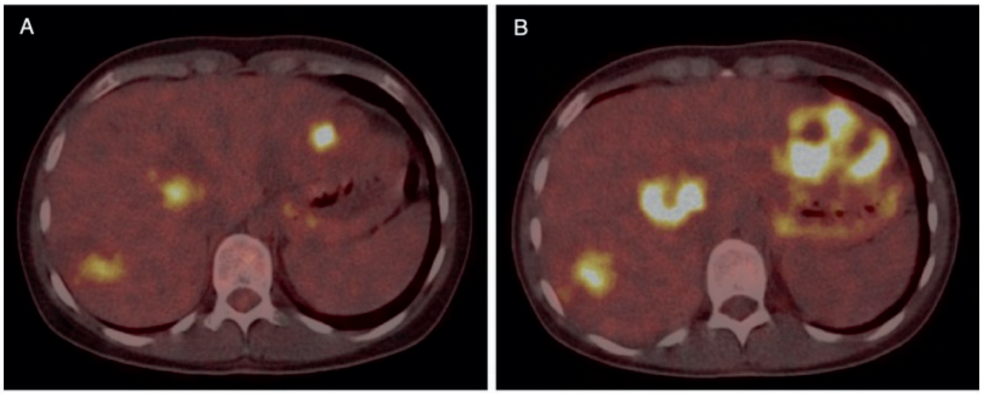

Figure 3: (A) ^{18}F-FDG-PET/CT of a GIST patient with a KIT exon 11 mutation, after 3 weeks of treatment with imatinib 800 mg. (B) Metabolic progression observed after 7 months of treatment with imatinib 800 mg daily, resulting in change of systemic treatment to sunitinib 37.5 mg daily.

Change in management was mainly a result of non-response or progression. Change in management was mostly surgical and resulted in 36% of the cases in a metastasectomy. Interestingly, no difference in PFS was found between non-responders and responders. This suggests that change in management in non-responders might have been effective.

Our results hence suggest that conducting an ^{18}F-FDG-PET/CT scan later in treatment might result in prolonged first line treatment with imatinib. However, considering the retrospective nature of this study, it is reasonable to assume that these outcomes can be a result of selection bias. In our current daily clinical practice, we do not routinely perform ^{18}F-FDG-PET-CT in metastatic GIST patients and based on our findings we would not recommend this.

In conclusion, in contrast to previous studies suggesting a significant impact on ^{18}F-FDG-PET/CT in patients with metastatic GIST, early response evaluation using ^{18}F-FDG-PET/CT does not influence treatment decisions in these patients. ^{18}F-FDG-PET/CT can be useful in case of indeterminate CT results or when for specific predefined indications a response evaluation is needed later in treatment.

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