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

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Chapter 4

Nuclear imaging

Paragraph 4.1

Early evaluation of response using ^{18}F-FDG PET influences management in gastrointestinal stromal tumor patients treated with neoadjuvant imatinib

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Abstract

Objective

^{18}F-FDG PET has previously been proven effective as an early way to evaluate the response of gastrointestinal stromal tumors (GISTs) to imatinib treatment. However, it is unclear whether early evaluation of response affects treatment decisions in GIST patients treated with neoadjuvant intent.

Methods

We retrospectively scored changes in management based on early evaluation of response by ^{18}F-FDG PET in patients in the Dutch GIST registry treated with neoadjuvant imatinib.

Results

Seventy ^{18}F-FDG PET scans were obtained for 63 GIST patients to evaluate for an early response to neoadjuvant imatinib. The scans led to a change in management in 27.1% of the patients. Change in management correlated strongly with lack of metabolic response ($P < 0.001$) and non–*KIT* exon 11–mutated GISTs ($P < 0.001$).

Conclusion

Performing ^{18}F-FDG PET for early evaluation of response often results in a change of management in GIST patients harboring the non–*KIT* exon 11 mutation and should be considered the standard of care in GIST patients treated with neoadjuvant intent.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors arising from the gastrointestinal tract. In local disease, surgery is the primary treatment of choice. In advanced GISTs, treatment with imatinib—a tyrosine kinase inhibitor that targets Bcr-ABL, c-KIT, and platelet-derived growth factor a (*PDGFRA*)—has resulted in spectacular responses. Depending on the type of driver mutation, the partial response rate is up to 84% (in the case of a mutation in *KIT* exon 11).(1,2) When complete resection is not feasible or would result in serious morbidity, neoadjuvant treatment with imatinib is advised until maximum response is achieved.(3,4) Whereas a volume response measurable by CT often requires 6–9 months of imatinib treatment, previous studies have shown that a metabolic response measured by ^{18}F-FDG PET can already predict imatinib responses within 1–8 d.(5–7) International guidelines therefore recommend early evaluation of response using ^{18}F-FDG PET in GIST patients treated with neoadjuvant intent.(3) By this means, patients without a metabolic response can be referred directly to surgery within 1–2 wk. Early evaluation by ^{18}F-FDG PET hence offers an opportunity to adjust and optimize treatment strategies in GIST patients treated with neoadjuvant intent. We aimed to assess to what extent management of these patients in clinical practice is influenced by the findings of ^{18}F-FDG PET.

Methods

^{18}F-FDG PET/CT scans obtained for patients in the Dutch GIST Registry were evaluated. The registry includes all patients diagnosed with GIST between January 2009 and October 2016 in the 5 GIST centers in The Netherlands: Netherlands Cancer Institute–Antoni van Leeuwenhoek, Leiden University Medical Center, Erasmus University Medical Center, Radboud University Medical Center Nijmegen, and University Medical Center Groningen. Data acquisition was approved by the local independent ethics committees and was in accordance with the Declaration of Helsinki.

The analysis included the ^{18}F-FDG PET scans of patients treated with imatinib with neoadjuvant intent. Early evaluation of response is defined as an evaluation within 8 weeks after the initiation of medical treatment or a change in its dose or type. Change in management was defined as a difference between the pre-PET and post-PET treatment strategies. Four categories of management change were defined: change in surgical management (e.g., surgery performed, postponed, or cancelled), change in systemic treatment (e.g., stopping, switching, or changing the dose), change in treatment objective (e.g., from curative to palliative), and change in management regarding a secondary tumor (e.g., diagnosis, resection, or treatment of a second tumor based on a PET result). Responses were derived from radiologic reports and, in general, were qualitatively categorized as complete, partial, or none.

Demographic and biologic characteristics such as sex, age, tumor size, tumor location, and tumor mutation status were derived from the Dutch GIST Registry. Statistical analyses were conducted using IBM SPSS Statistics 23. To assess an association between change in management and demographic and biologic characteristics, Pearson Chi-square (x^2) analyses were used for categoric variables and Mann–Whitney U tests were used for continuous variables. All tests were 2-sided, and a p-value of less than 0.05 was considered significant.

Results

Of the 781 patients in the database, 259 underwent ^{18}F-FDG PET—a total of 404 scans, of which 234 were obtained at base-line. Of the 170 PET scans obtained for treatment evaluation, 70 scans in 63 patients treated with neoadjuvant intent were considered to have been obtained for early evaluation of response. This number corresponds to 31% of the 202 patients in the database who had been treated with neoadjuvant intent. In all patients, treatment began with imatinib: 400 mg in 60 patients and 800 mg in 3 patients with *KIT* exon 9–mutated GIST. The patient characteristics are described in Table 1.

A metabolic response was seen in about 70% of PET scans, and a change in management in 27% (Table 2). A change in management correlated strongly with a lack of metabolic response (Pearson x^2, $p < 0.001$) and harboring of a mutation outside *KIT* exon 11 (Pearson x^2, $p < 0.001$) (Figure 1). Also, mutational status and response correlated strongly with each other (Pearson x^2, $p < 0.001$). Of 29 PET scans of GISTs with a non–*KIT* exon 11 mutation, 15 (52%) led to a change in management: 2 of 2 scans for *KIT* exon 13, 3 of 5 for *PDGFRA* 18, 4 of 7 for *KIT* and *PDGFRA* wild-type, and 6 of 12 for GISTs with an unknown mutation. No change in management was seen in the 3 patients with a KIT exon 9 mutation. For *KIT* exon 11–mutated GISTs, a change was seen in 3 of 41 scans (7%).

Of the 15 PET results that led to a change in management in non–*KIT* exon 11–mutated GISTs, a change in surgical management was seen once (3%), a change in systemic treatment was seen 6 times (21%; 3 regarding a switch to sunitinib and 3 regarding dose), both a change in dose and early planned surgery were seen 7 times (24%), and a second tumor necessitating treatment adaptation was seen once (3%). Three of the 41 PET scans of *KIT* exon 11 GIST patients led to a change in management: 2 times, the change involved systemic treatment (a dose increase after persistence of metabolic activity in parts of the tumor), and once, the change was due to discovery of a second primary tumor. No change in treatment objective was seen.

Change in systemic treatment led to improved metabolic response 2 times: once in a *KIT* exon 11–mutated GIST and once in a GIST with an unknown mutation. Early surgery resulted in R0 resections in 5 of 8 patients, and 1 patient had an R1 resection with ongoing disease-free survival at 61 months of follow-up. Peri-operative metastatic disease was revealed in 2 patients: 1 patient with wild-type GIST died of disease progression, and

1 patient with *PDGFRA* exon 18 (non-D842V) underwent debulking surgery with ongoing disease-free survival under imatinib treatment.

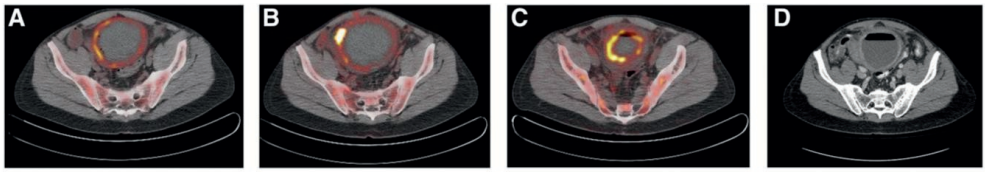

Figure 1: ^{18}F-FDG PET/CT in GIST patient with *KIT* exon 13 mutation.

(A) Baseline PET/CT image (SUV_{max} = 4.3). (B) PET/CT image after 2 weeks of treatment, showing both metabolic progression (SUV_{max} = 6.7) and size progression. Imatinib dose was increased from 400 to 800 mg daily. (C) PET/ CT image 4 weeks after increase of dose, showing notable response in size. However, because of persisting metabolic activity (SUV_{max} = 4.4) and increased symptomatology, early resection of tumor was performed. (D) CT image showing notable response in size after dose increase. R0 resection was performed, resulting in ongoing disease-free survival.

Table 1: Patient and tumor characteristics.

Characteristic	**Patients (*n* = 63)**
Sex	
Male	40 (63.5%)
Female	23 (36.5%)
Median age (y)	61 (range, 15–87)
Location of primary tumor	
Stomach	46(73.0%)
Small bowel	6(9.5%)
Duodenum	5(7.9%)
Rectum	5(7.9%)
Esophagus	1(1.6%)
Median primary tumor size (mm)	106 (range, 19–300)
Mitotic index	
>5 per 5 mm^2	40 (63.5%)
<5 per 5 mm^2	13 (20.6%)
Not reported	10 (15.9%)
Mutation status	
KIT exon 11	41 (65.1%)
KIT exon 9	2 (3.2%)
KIT exon 13	1 (1.6%)
PDGFRA exon 18	5 (7.9%)
Wild-type	7 (11.1%)
Not determined	7 (11.1%)

Table 2: ^{18}F-FDG PET/CT results before and after neoadjuvant imatinib treatment and resulting changes in management.

Result/change	**PET/CTs (*n* = 70)**
Baseline PET available?	
Yes, ^{18}F-FDG–avid	64 (91.4%)
Yes, not ^{18}F-FDG–avid	3(4.3%)
No	3 (4.3%)
Baseline resulted in change in management?	
Yes, change in treatment objective	3 (4.3%)
Yes, change regarding second tumor	3 (4.3%)
No change in management	61 (87.1%)
No baseline available	3 (4.3%)
Metabolic response?	
Yes, complete	20 (28.6%)
Yes, partial	30 (42.9%)
No	14 (20.0%)
No baseline available or no ^{18}F-FDG avidity at baseline	6 (8.6%)
Change in management (any)?	
Yes	18 (27.1%)
No	52 (72.9%)
Change in surgical management?	
Yes	8 (11.4%)
No	62 (88.6%)
Change in systemic treatment?	
Yes	15 (21.4%)
No	55 (78.6%)
Change in treatment objective?	
Yes	0 (0%)
No	70 (100%)
Change regarding second tumor?	
Yes	2 (2.9%)
No	68 (97.1%)

Discussion

Previous studies have shown that ^{18}F-FDG PET is a sensitive method of evaluating early response to treatment with tyrosine kinase inhibitors in GIST patients.(8–11) International guidelines recommend early assessment of response using ^{18}F-FDG PET in patients treated with neoadjuvant intent to prevent delay of surgery.(3) Also, early evaluation using ^{18}F-FDG PET is thought to optimize individual treatment.(5) However, to our knowledge, no study has assessed the actual influence of ^{18}F-FDG PET on treatment strategies. We showed that in 27% of cases, ^{18}F-FDG PET led to a change of management in GIST patients treated with neoadjuvant imatinib.

In GIST patients harboring a mutation other than *KIT* exon 11, a change in management was seen in over half the cases. Early assessment of response led to surgery with curative intent in all patients. However, 2 patients had perioperative metastatic disease that was not seen on either CT or ^{18}F-FDG PET. In all but 1 case, early surgery led to ongoing disease-free survival, implying that early evaluation by ^{18}F-FDG PET prevented progressive and unresectable disease. However, the retrospective nature of this study and the heterogeneous follow-up times are a major limitation to further interpretation of these results. In addition, the responses were evaluated by different nuclear physicians, potentially causing heterogeneous definitions of response.

Conclusion

In this nationwide series of imatinib-treated GIST patients harboring non–*KIT* exon 11 mutations, ^{18}F-FDG PET scans obtained for early evaluation of response in the neoadjuvant setting resulted in a change in management in half the cases. We therefore recommend that evaluation with ^{18}F-FDG PET be considered in this curative setting.

Disclosure

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References

1. Heinrich MC. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21:4342–4349.
2. Szucs Z, Thway K, Fisher C, et al. Molecular subtypes of gastrointestinal stromal tumors and their prognostic and therapeutic implications. Future Oncol. 2017;13: 93–107.
3. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(suppl 3):iii21–iii26.
4. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN task force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw. 2010;8(suppl 2):S1–S41.
5. Prior JO, Montemurro M, Orcurto M-V, et al. Early prediction of response tosunitinib after imatinib failure by 18F-fluorodeoxyglucose positron emission to-mography in patients with gastrointestinal stromal tumor. J Clin Oncol. 2009; 27:439–445.
6. Stroobants S, Goeminne J, Seegers M, et al. 18FDG-positron emission tomogra-phy for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). Eur J Cancer. 2003;39:2012–2020.
7. Malle P, Sorschag M, Gallowitsch HJ. FDG PET and FDG PET/CT in patients with gastrointestinal stromal tumors. Wien Med Wochenschr. 2012;162:423– 429.
8. Choi H. Response evaluation of gastrointestinal stromal tumors. Oncologist. 2008;13(suppl 2):4–7.
9. Holdsworth CH, Badawi RD, Manola JB, et al. CT and PET: early prognostic indicators of response to imatinib mesylate in patients with gastrointestinal stro-mal tumor. AJR. 2007;189:W324–W330.
10. Stefanelli A, Treglia G, Mirk P, Muoio B, Giordano A. F-FDG PET imaging in the evaluation of treatment response to new chemotherapies beyond imatinib for patients with gastrointestinal stromal tumors. ISRN Gastroenterol. 2011;2011: 824892.
11. Treglia G, Mirk P, Stefanelli A, Rufini V, Giordano A, Bonomo L. 18F-fluorodeoxyglucose positron emission tomography in evaluating treatment response to imatinib or other drugs in gastrointestinal stromal tumors: a systematic review. Clin Imaging. 2012;36:167–175.