

Serial ^{18}F -FDG PET for Monitoring Treatment Response After Allogeneic Stem Cell Transplantation for Myelofibrosis

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Our objective was to assess the feasibility of ^{18}F -FDG PET/CT for noninvasive monitoring of treatment response after allogeneic stem cell transplantation (SCT) for myelofibrosis. **Methods:** Twelve patients with myelofibrosis underwent ^{18}F -FDG PET/CT before and after SCT. Bone marrow uptake, spleen uptake, and spleen size were assessed before and after SCT and compared with hematologic response criteria and bone marrow biopsies. **Results:** All patients who did not achieve complete remission remained PET-positive ($P = 0.02$). Extent of disease, bone marrow metabolism, spleen metabolism, and spleen volume decreased significantly in patients with complete remission ($P = 0.03$). PET/CT after SCT had a sensitivity of 1.0 (95% confidence interval [CI], 0.54–1.0), a specificity of 0.83 (95% CI, 0.36–1.0), a negative predictive value of 1.0 (95% CI, 0.48–1.0), and a positive predictive value of 0.86 (95% CI, 0.42–1.0) for diagnosis of residual disease. **Conclusion:** ^{18}F -FDG PET/CT is feasible for noninvasive monitoring of treatment response after allogeneic SCT for myelofibrosis.

Key Words: myelofibrosis; stem cell transplantation; allogeneic; positron emission tomography; ^{18}F -FDG PET/CT

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Myelofibrosis is a *BCR-ABL1*-negative hematopoietic stem cell disorder characterized by marked bone marrow inflammation, reactive marrow fibrosis replacing normal hematopoiesis, and consecutive extramedullary hematopoiesis (1,2). The only potentially curative treatment approach is allogeneic hematopoietic stem cell transplantation (SCT), leading to 5-y survival rates of 51%–61% (3). A noninvasive imaging-derived surrogate parameter for bone marrow involvement would be desirable not only for initial evaluation of disease extent but also for monitoring and adjustment of therapy.

A recent study has demonstrated the feasibility of ^{18}F -FDG PET/CT for noninvasive visualization and quantitation of the extent and activity of bone marrow involvement in a cohort of patients before SCT (4). In that study, the metabolic activity of the

bone marrow as determined by ^{18}F -FDG PET was significantly associated with the histopathologic grade of fibrosis, and the extent of disease on PET decreased with time after diagnosis. These results suggest that PET may also be suitable for therapy monitoring. Typically, invasive histopathology shows rapid regression of fibrosis after SCT (5). A recent report indicated that the bone marrow signal on ^{18}F -FDG PET normalizes after SCT (6).

Therefore, the aim of this study was to assess the feasibility of ^{18}F -FDG PET/CT for monitoring therapy response in myelofibrosis patients undergoing SCT.

MATERIALS AND METHODS

Study Population

We retrospectively analyzed data from 12 patients (10 men and 2 women; median age, 62.9 y; 95% confidence interval [CI], 60.8–67.4 y) with primary ($n = 9$) or secondary ($n = 3$) myelofibrosis. This was a feasibility study. Therefore, no power analysis or sample size justification was provided. The purpose of this pilot study was to generate the hypotheses for verification in future studies. The patients underwent an ^{18}F -FDG PET/CT scan between October 2010 and October 2014 to assess the bone marrow compartment before (PET1) and after (PET2) SCT. All fulfilled the criteria of the World Health Organization diagnostic for myelofibrosis or the criteria of the International Working Group for Myelofibrosis Research and Treatment for secondary myelofibrosis (7,8). The study was approved by the Clinical Institutional Review Board of University Medical Center Hamburg–Eppendorf (WF-008/13). Written informed consent was obtained from all subjects.

Reference Standard

A panel of clinical and hematologic parameters was evaluated in all patients. The interval between PET/CT and assessment of hematologic parameters was less than 2 wk. Bone marrow biopsies were obtained from the posterior iliac crests, and fibrosis was graded on a 4-point scale (9).

The remission status was determined using the Revised Response Criteria for Myelofibrosis (10). Patients were followed for 1,324 d (95% CI, 642–1,681 d) after SCT.

PET/CT Acquisition and Image Reconstruction

^{18}F -FDG PET/CT imaging was performed on a Gemini GXL10 scanner (Philips) using a standard whole-body protocol as described before (4).

Image Analysis, Quantification of Metabolic Activity, and PET Response Assessment

Two interpreters masked to all clinical information analyzed all images in consensus.

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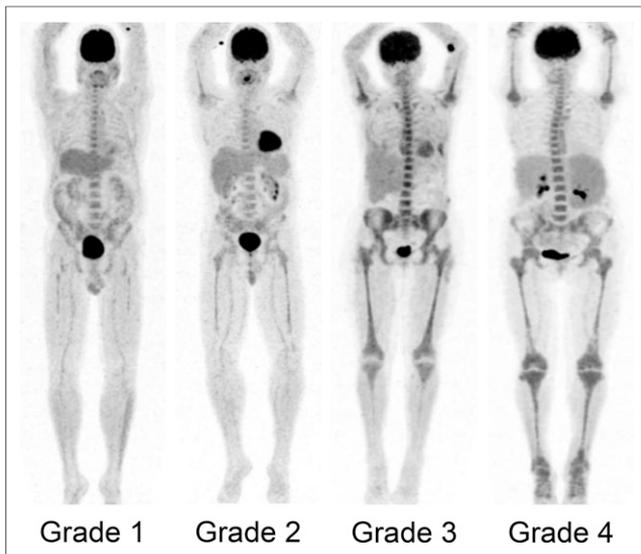


FIGURE 1. Grading of extent of bone marrow uptake on maximum-intensity-projection PET images.

Osseous ^{18}F -FDG Uptake and PET Response Assessment. The pattern of ^{18}F -FDG accumulation was analyzed on maximum-intensity-projection images for each patient (Fig. 1), and the extent of ^{18}F -FDG accumulation was graded on a 5-point scale to assess changes in the extent of bone marrow involvement (4). Grade 4 indicated increased uptake in the central skeleton and the extremities extending into the small bones of the feet; grade 3, markedly increased uptake in the central skeleton and the extremities, extending into the tibial bone; grade 2, markedly increased uptake in the central skeleton and the proximal extremities, extending into the distal half of the femoral bone; and grade 1, mildly increased uptake in the central skeleton and the proximal extremities. Absence of uptake in the peripheral skeleton was consistent with grade 0.

Bone marrow SUV_{max} was measured using an oval region of interest at least 15 mm in diameter placed on coregistered PET/CT images within L1 to L4 as described before (4). The final bone marrow SUV_{max} results were produced by averaging the measurements for all 4 vertebrae. Lumbar bone marrow SUV_{max} has previously been shown to be inversely correlated with the histopathologic grade of bone marrow fibrosis (4).

Spleen ^{18}F -FDG Uptake and Spleen Volume. The SUV_{mean} of the spleen was determined by averaging the results of region-of-interest measurements on 3 nonadjacent slices. The area of the spleen on each slice was multiplied by the slice thickness to obtain the spleen volume on breath-hold CT.

Diagnosis of metabolic complete response (CR) required complete resolution of bone marrow uptake in peripheral bones, stable or decreased uptake in lumbar vertebrae, stable or decreased spleen uptake, and decreased (not necessarily normalized) spleen volume. In particular, residual grade 1 bone marrow uptake, increasing bone marrow SUV_{max} , or an increase in spleen metabolism or volume was considered absence of metabolic CR.

Statistical Analysis

Continuous variables are expressed as median with 95% CI. Categorical variables are presented with absolute and relative frequencies. Continuous data were compared using the Wilcoxon matched-pairs signed-rank test. For categorical variables, P values were computed from contingency tables using the Fisher exact test. The Spearman correlation coefficient, r_s , was used to correlate imaging findings with grade of bone marrow fibrosis.

The Mann–Whitney test was used to compare baseline PET data between patients reaching CR and those who did not. Survival probabilities were estimated using the Kaplan–Meier method, and strata were compared using the Gehan–Breslow–Wilcoxon method. Follow-up time was calculated as the time from SCT until death or last follow-up date. Statistical significance was established for P values of less than 0.05. Statistical analysis was performed using Prism (version 6.0; GraphPad) for Windows (Microsoft).

RESULTS

Patient characteristics are reported in Table 1 (more detailed data are available in the supplemental materials available at <http://jnm.snmjournals.org>). All patients underwent ^{18}F -FDG PET/CT within 9 d (95% CI, 6–12 d) before allogeneic SCT (PET1) and at 223 d (95% CI, 100–442 d) after SCT (PET2). At the time of PET2, 6 patients (50%) had achieved CR (2 of them fulfilled the criteria for molecular remission), 4 patients (33%) had achieved partial remission, 1 patient (8%) had progressive disease, and 1 patient (8%) had relapse.

All 12 patients demonstrated increased bone marrow uptake on PET1. At PET2, 5 of 6 patients (83%) with CR became PET-negative (PET metabolic CR). One patient (17%) fulfilled the criteria for CR but had residual histologic grade 1 marrow fibrosis and remained PET-positive, but the extent of bone marrow involvement on PET decreased from grade 3 to grade 1. All patients who did not achieve CR remained PET-positive ($P = 0.02$). In the patients who achieved CR, extent of disease ($P = 0.03$), bone marrow SUV_{max} ($P = 0.03$), spleen metabolism ($P = 0.03$), and spleen volume ($P = 0.03$) decreased significantly from PET1 to PET2. Regression of bone marrow fibrosis on biopsies correlated significantly with regression of bone marrow SUV_{max} ($r_s = -0.77$, $P < 0.003$). Data on extent of disease, bone marrow SUV_{max} , spleen metabolism, and spleen volume before and after SCT are shown in Table 2.

PET2 had a sensitivity of 1.0 (95% CI, 0.54–1.0), a specificity of 0.83 (95% CI, 0.36–1.0), a negative predictive value of 1.0 (95% CI, 0.48–1.0), and a positive predictive value of 0.86 (95% CI, 0.42–1.0) for diagnosis of residual disease. Imaging examples of patients before and after SCT are shown in Figures 2 and 3.

TABLE 1
Patient Characteristics ($n = 12$)

Parameter	Value
Subjects (n)	12 (100%)
Median age (y)	62.9
95% CI	60.8–67.4
Sex (M/F)	10 (83%)/2 (17%)
Type of myelofibrosis	
Primary	9 (75%)
Secondary	3 (25%)
Remission status at PET2	
Complete remission	6 (50%)
Partial remission	4 (33%)
Progressive disease	1 (8%)
Relapse	1 (8%)

TABLE 2
Disease Extent, Bone Marrow Metabolism, Spleen Metabolism, and Spleen Volume on ¹⁸F-FDG PET/CT Before and After SCT (*n* = 12)

Status	Bone marrow					Spleen*					
	Median disease extent		SUV _{max}			Volume			SUV _{mean}		
	PET1	PET2	PET1	PET2	Δ	PET1	PET2	Δ	PET1	PET2	Δ
CR	3 (1–4)	0 (0–1)	3.2 (2.0–4.3)	2.0 (1.8–2.5)	–37%†	1,744 (606–4,005)	551 (231–1,277)	–68%†	2.3 (1.8–3.5)	1.8	–22%†
PR	1 (1–4)	3 (1–3)	2.3 (2.2–2.4)	2.5 (2.0–5.6)	+9%	2,784 (1,977–3,601)	1,404 (944–2,417)	–50%	2.5 (2.2–2.6)	1.9 (1.5–2.4)	–24%
PD	1	1	2.2	2.3	+5%	3,761	3,128	–17%	2.6	2.1	–19%
Relapse	1	1	3.4	2.8	–18%	NA	NA	NA	NA	NA	NA

*One patient with relapse was splenectomized.

†Statistically significant.

PR = partial remission; PD = progressive disease; NA = not applicable.

Data are median followed by 95% CIs in parentheses.

On PET1, there was no significant difference in extent of disease ($P = 0.24$), bone marrow SUV_{max} ($P = 0.19$), spleen volume ($P = 0.18$), or spleen metabolism (SUV_{mean}, $P = 0.75$) between patients who achieved CR and those who did not.

In patients with metabolic CR on PET2, there was a trend toward increased overall survival, with a hazard ratio of 0.11 (95% CI, 0.01–1.05; $P = 0.06$ [Gehan–Breslow–Wilcoxon test]), but this trend did not reach statistical significance (Fig. 4).

DISCUSSION

In the present study, we demonstrated the feasibility of ¹⁸F-FDG PET/CT for monitoring treatment response after SCT for myelofibrosis. Most patients (83%) who achieved CR after SCT demonstrated a complete metabolic remission on PET2, indicating that the bone marrow signal in myelofibrosis is influenced by therapeutic interventions. PET was false-positive in one patient with CR, but that patient had residual histologic grade 1 marrow fibrosis, which was allowed in the definition of CR. In other cases, persistent bone marrow uptake may also be caused by bone marrow activation induced by infection or drugs such as granulocyte-colony-stimulating factor.

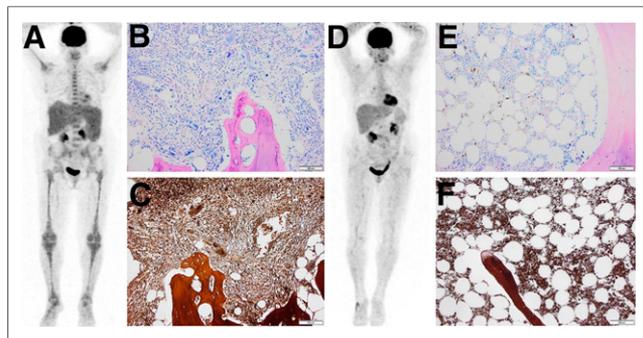


FIGURE 2. ¹⁸F-FDG PET/CT scans before (A) and after (D) SCT, showing metabolic CR. Initial biopsy showed proliferation of enlarged megakaryocytes and enhanced granulopoiesis (B, Giemsa staining), accompanied by bone marrow fibrosis (C, Gomori staining). After SCT, cellularity was normalized, atypical megakaryocytes had vanished (E), and no fibrosis was present (F).

PET correctly identified all patients who did not achieve CR after SCT ($P = 0.02$), yielding a high sensitivity of 100%, indicating that a positive PET scan after SCT may indicate residual disease. The performance of PET/CT in myelofibrosis was comparable to that for other hematologic diseases. A recent study demonstrated a high negative predictive value of 95% for assessment of progression or early relapse after first-line chemotherapy in advanced-stage Hodgkin lymphoma (11). In view of these data, it is tempting to speculate that PET may be able to replace or complement invasive hematologic reevaluation in selected myelofibrosis patients. In other hematologic malignancies such as multiple myeloma, persistently increased bone marrow uptake has been shown to be able to identify residual or recurrent disease (12). Interestingly, in contrast to the patients with CR, those patients who achieved only a partial remission did not have statistically significant quantitative changes in spleen metabolism, bone marrow metabolism, or spleen volume.

Bone marrow biopsies are associated with pain and bleeding, particularly in cytopenic patients. Sampling error is a frequent problem in bone marrow biopsy, particularly because fibrosis is an inhomogeneous process with variable distribution (5). PET can estimate bone marrow involvement and its distribution on whole-body images (4). Since bone marrow SUV_{max} has been shown to correlate with the histologic grade of fibrosis (4), PET may be used to guide bone marrow biopsies to identify the region with the most prominent fibrotic activity. Given that repeated biopsies are mandatory for reevaluation of the grade of fibrosis after therapy, PET may represent a noninvasive alternative to repeated

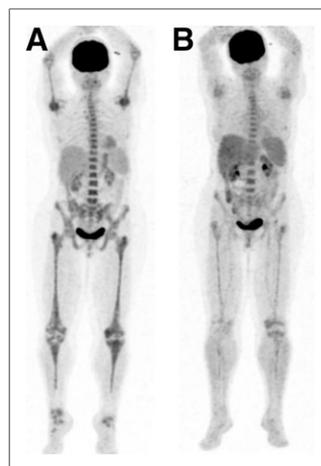


FIGURE 3. ¹⁸F-FDG PET/CT before (A) and after (B) SCT. Partial remission is seen, with persistent uptake on PET.

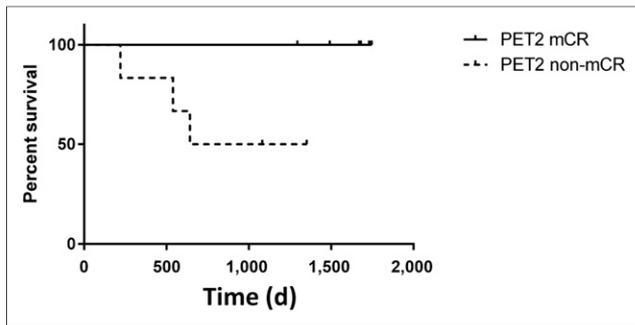


FIGURE 4. Kaplan–Meier plot of overall survival. Trend toward increased overall survival in patients with metabolic CR (mCR) on PET2 did not reach statistical significance ($P = 0.06$).

invasive biopsies. However, the ^{18}F -FDG accumulation in bone marrow is influenced by both inflammatory activity and myelopoiesis. Other PET tracers such as the proliferation marker ^{18}F -fluorodeoxythymidine may help us to better understand the different aspects of bone marrow disease.

The major limitation of this retrospective study was the small number of patients. Therefore, the statistical power to assess the precise predictive value of PET was limited. In addition, a more standardized protocol (e.g., PET2 at 100 d after SCT) might have shown clearer associations. Recent studies have indicated that MRI allows monitoring of the response or progression of marrow disease (5). Further studies are needed to compare the relative performance of PET/CT and MRI for assessment of treatment response.

CONCLUSION

This retrospective study demonstrated that ^{18}F -FDG PET/CT is feasible for noninvasive monitoring of myelofibrosis treatment response after allogeneic SCT. Response-adapted therapy guided by PET for myelofibrosis patients may be a promising approach that should be further evaluated in prospective clinical trials.

DISCLOSURE

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