Leukemia Research 37 (2013) 1057–1062

Contents lists available at SciVerse ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

# The role of $^{18}$F-FDG PET/CT for the diagnosis of infections in patients with hematological malignancies and persistent febrile neutropenia

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ARTICLE INFO

*Article history:*
Received 21 April 2013
Received in revised form 11 June 2013
Accepted 17 June 2013
Available online 10 July 2013

*Keywords:*
Febrile neutropenia
PET/CT
Hematological malignancies
FDG
Invasive fungal infections

ABSTRACT

We assessed the performance of PET/CT for diagnosis and management of infections in high-risk hematological cancer patients with persistent febrile neutropenia in a prospective study. $^{18}$F-FDG PET/CT with contrast-enhanced CT was performed on day 5–7 of persistent fever. Between 2008 and 2011, 91 PET/CT examinations were performed for different episodes in 79 patients, resulting in 117 diagnoses. The sensitivity of the PET/CT was 79.8% (71/89) compared to 51.7% (46/89) with chest/sinus CT alone. Specificities were 32.14% (9/28) vs. 42.85% (12/28), respectively. PET/CT resulted in a change from the pre-test diagnosis in 63/91 (69%) of episodes and in modification of patients' management in 46/91 (55%). PET/CT was beneficial in diagnosing abdominal infections. PET/CT has a potential role in the diagnostic evaluation of patients with persistent febrile neutropenia.



## 1. Background

Infections are an important cause of morbidity and mortality in high-risk hematological cancer patients [1]. We currently lack the ability to diagnose these infections early enough, leading to empirical over-treatment and imprecise treatment.

18-Fluoro-2-deoxy-D-glucose positron emission tomography ($^{18}$F-FDG-PET) is emerging as an important aid in the investigation of fever of unknown origin (FUO) in non-immune-compromised patients [2–4]. $^{18}$F-FDG is taken up by metabolically active cells with high glucose consumption: neutrophils, lymphocytes and activated macrophages [5]. It accumulates in malignant tissues and at sites of infection and inflammation. When combined with contrast enhanced CT (PET/CT), more precise localization and characterization of the pathological FDG uptake is possible. The advantages of PET/CT over other imaging include the diagnosis of vascular infections, bone infections, and FUO [2,6,7]. As such it could prove a valuable addition to the diagnostic evaluation of patients with persistent febrile neutropenia, depending on whether FDG uptake is sensitive enough in patients with a very low neutrophil count.

We aimed to assess the performance of FDG-PET combined with diagnostic CT for diagnosis of IFIs and other infections in high-risk hematological cancer patients with febrile neutropenia and persistent or breakthrough fever. We compared the performance of PET/CT with that of a chest and sinus plain CT, since this is the currently recommended radiological evaluation for suspected IFI among these patients [8,9].

## 2. Patients and methods

### 2.1. Participants

The study was conducted in the Hemato-oncology and Bone Marrow Transplant Units at Davidoff's Cancer Center, Beilinson Hospital, Rabin Medical Center. The center is a university affiliated, primary and tertiary care center for adult patients (>18 years). Patients with acute leukemia or aggressive lymphoma undergoing chemotherapy, allogeneic or autologous HCT with persistent fever or breakthrough fever during neutropenia (<500/mm$^3$) and broad-spectrum antibiotics were eligible. Breakthrough fever could include persistence or re-appearance of fever at days

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http://dx.doi.org/10.1016/j.leukres.2013.06.025

5–7 of antibiotic treatment, with or without microbiological documentation of the initial febrile episode. Patients with lymphoma were included only if they had a baseline PET/CT to compare with. Antibiotic prophylaxis consisting of ciprofloxacin was administered to all patients from neutropenia onset. Antifungal prophylaxis consisting of fluconazole was administered to all leukemia, allogeneic and autologous HCT patients. Piperacillin–tazobactam or ceftazidime were given empirically for febrile neutropenia. For persistent or breakthrough fever, blood cultures were repeated and a galactomannan assay was performed. As per local guidelines, both empirical and preemptive antifungal therapy were permitted for persistent febrile neutropenia [10]. All patients fulfilling inclusion criteria and providing written informed consent were consecutively enrolled between January 2008 and January 2011. Patients could be included more than once in the study for different episodes of persistent febrile neutropenia. The study was prospective and results of the PET/CT were available to clinicians in real time. The study was approved by the local ethics committee.

### 2.2. Reference standard

The reference standard was the final diagnosis for the episode 30 days after neutropenia resolution or at the time of death if occurring before. The final diagnosis was adjudicated by a hematologist and an infectious diseases expert reviewing all clinical, microbiological and radiological data at the final follow-up. The evaluators were not blinded to the PET/CT results. No post-mortem examinations were performed. Final diagnoses were classified as infectious; fever of unknown origin (FUO) when no infectious process was found; fever due to the primary malignancy; or due to other non-infectious causes. Infectious diagnoses were classified into bacteremia, microbiologically documented infections (MDIs), clinically documented infections (CDIs) or invasive fungal infections (IFIs), using established definitions [11]. IFIs were defined according to the 2008 revised criteria [12]. The specific type of infection under each category was documented as well (e.g. central-catheter-related bloodstream infection, skin abscess, etc.) using the recommended definitions for healthcare-associated infections [13]. Each episode was allowed to have more than one diagnosis.

### 2.3. Index test

$^{18}$F-FDG PET/CT was performed using an integrated PET/CT scanner (Discovery STE, GE Medical Systems, Milwaukee, WI). $^{18}$F-FDG dose varied from 370 to 666 MBq (10–18 mCi) according to patient's weight and 800–1000 mL of diluted iodinated contrast material was administered orally for bowel opacification. Due to infection control considerations injection of $^{18}$F-FDG was performed in patients' rooms and after 60 min the patients were transferred to the PET/CT scanner wearing a N-95 mask.

Chest CT was performed with patients asked to hold their breath with tube voltage of 120 kVp, spiral CT at 0.8 s per rotation, 100 mA s, section thickness of 3.75 mm, and 3.75 mm interval with image reconstruction every 2.5 mm. Contrast-enhanced CT was performed from top of the head to the toes with tube voltage of 120 kVp, spiral CT at 0.8 s per rotation with modulated 40–300 mA s, section thickness of 3.75 mm, and 3.75 mm interval with image reconstruction every 2.5 mm. Iodine contrast media (Ultravist 300; iopromide 0.623 g/ml, Bayer Schering Pharma AG, Berlin, Germany; 1.5 cm$^3$/kg) was intravenously administered in all examinations, except for patients with iodine hypersensitivity and renal insufficiency. PET emission images were obtained using a weight-based protocol, with 3 min of acquisition time per bed position. Five to six bed positions from skull base to mid-thigh resulted in an acquisition time of 18–24 min. All PET images were reconstructed using an iterative algorithm, with CT-based attenuation correction applied.

Blinded evaluation was performed separately for the chest and sinus CT and the full PET/CT scan by a radiology and nuclear medicine expert, respectively. PET/CT evaluators were blinded to the patients' final diagnosis.

### 2.4. Data collection

We prospectively collected patient data from the time of study entry until end of follow-up at 30 days or death. Data included all clinical, laboratory, microbiological and radiological findings, caring physicians' diagnoses, all antimicrobial treatment and interventions. We assessed the contribution of PET/CT to diagnosis: we recorded a change in diagnosis or an additional diagnosis (identification of the presence of infection in cases regarded before as FUO, new sites of infection, extent of infection). In addition, we documented whether there was a modification in patient management following PET/CT (change in diagnostic work-up and therapy: antimicrobial and antifungal modification, surgery, removal of devices etc.)

### 2.5. Statistical analysis

Sensitivity and specificity of PET/CT were calculated per diagnosis, examining whether findings compatible with the diagnosis were observed on the examination. We similarly calculated the sensitivity and specificity of chest and sinus CT alone and total body CT (without the FDG uptake component). For sensitivity analysis the denominator was all infectious diagnoses; for specificity analysis the denominator included FUO, fever due to malignancies and other non-infectious diagnoses.

**Table 1**
Baseline characteristics of included patients and episodes.

| Characteristic | *N* |
|---|---|
| *Per patient* | |
| Number of patients | 79 |
| Age, median (range) | 56 (range: 21–85) |
| Gender (M/F) | 45/34 |
| *Per febrile episode* | |
| Number of episodes | 91 |
| *Underlying disease and status during the febrile episode* | |
| Acute myeloid leukemia (AML): | 52 |
| • Receiving chemotherapy | 48 |
| • No therapy | 4 |
| Acute lymphoblastic leukemia (ALL) | 17 |
| Allogeneic HCT[a] | 7 |
| Autologous HCT (all lymphoma)[a] | 7 |
| Lymphoma receiving chemotherapy | 7 |
| Hairy cell leukemia | 1 |
| *Data regarding the febrile episode* | |
| Days from last chemotherapy, median (range) | 10 (0–255) |
| Days of neutropenia < 500/mm$^3$, median (range) | 11 (5–100)[b] |
| Days of neutropenia < 100/mm$^3$, median (range) | 8 (0–37)[b] |
| Febrile days, median (range) | 6 (4–38) |
| Absolute neutrophil count, median (range) | 100 (0–5500)[c] |
| Days of antibacterial prophylaxis | 7 (0–42) |
| Days of antifungal prophylaxis | 11 (0–60) |
| *Previous episode of neutropenic fever* | 25 |

*Abbreviations.* ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FUO, fever of unknown origin; HCT, hematopoietic cell transplant.

[a] Eleven patients underwent allogeneic HCT (the transplantation preceded the febrile episode in seven) and eight patients underwent autologous HCT (seven preceding the febrile episode).

[b] Count refers to the absolute neutrophil count measured using automated blood counts; patients with apparently "normal" neutrophil counts were all neutropenic on visual examination of the blood smear. Does not include 5 episodes of prolonged neutropenia (more than a year) due to prior myelodysplastic syndrome (MDS).

[c] Includes 3 patients whose neutropenia resolved on the day of PET but fever persisted.

For primary bacteremia and central-line associated bloodstream infections (CLABSIs), we did not expect positive findings on PET/CT a priori. Thus, we also conducted a sensitivity analysis without counting them.

### 2.6. Sample size

The sample size was computed to allow for the demonstration of an advantage of PET/CT over chest/sinus CT. Based on preliminary data we assumed a disagreement between PET/CT and chest-sinus CT alone of 4% when the final diagnosis was no infection and 22% when the final diagnosis was infectious. A sample of 66 pairs afforded a power of 80% to detect a significant difference between PET/CT and the chest/sinus CT (2-sided McNemar test, alpha = 0.05). Assuming a 10% non-evaluability rate, we planned to recruit 74 patients to the study.

## 3. Results

### 3.1. Study population and reference standard diagnosis

Between January 2008 and January 2011, PET/CT examinations were performed in 79 patients for 91 episodes of persistent febrile neutropenia or breakthrough fever. Median age was 56 (range 21–85) years. Patients were neutropenic for a median of 11 (range 5–100) days. Most patients had acute leukemia (52 episodes in patients with acute myeloid leukemia and 17 episodes in patients with acute lymphoblastic leukemia). Patient characteristics and baseline data regarding the febrile episodes are depicted in Table 1.

The 30-day mortality rate was 16.5% (13/79 patients). Death was related to infection (as per the final diagnosis) in 11 patients, three of which had an IFI.

The final (reference standard) diagnoses included 89 infectious diagnoses: 62 bacterial infections (53% of all diagnoses) and 27 IFIs (23%). In addition, there were 13 diagnoses of fever due to the