^{18}F-FDG-PET/CT Imaging in Patients with Febrile Neutropenia and Haematological Malignancies

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Abstract. *The aim of the present study was to assess the prevalence of hyper-metabolic infection sites revealed by fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) positron-emission tomography (PET) combined with computed tomography (CT) in patients with febrile neutropenia (FN). Forty-eight consecutive patients with haematological malignancies and persistent FN (temperature ≥38˚C and neutrophil count <500 cells/μl for more than two days) as a consequence of intensive chemotherapy were prospectively included. Pathological FDG uptakes identified 31 foci of infections located in the lungs (n=15, 48.4 %), colon (n=4, 12.9%), pancreas (n=2, 6.5%), skin (n=3, 9.7%), ear-nose-throat area (n=5, 16.1%), central venous catheter tract (n=1, 3.2%) and gallbladder (n=1, 3.2%). These pathological FDG uptakes were observed in half of the 48 patients (n=24). Among the 38 patients with a clinical diagnosis of infection, 23 showed a pathological FDG uptake, resulting in a FDG-PET/CT sensitivity of 61% (95% CI, 43-76%). Our study confirmed the ability of FDG-PET/CT to diagnose infections in patients with persistent FN.*

Neutropenia is a major concern in the management of patients with cancer. It is particularly common in haematology, often secondary to chemotherapy. High-dose chemotherapy and treatment intensification (with haematopoietic stem cell transplant) have been increasingly used, and myelosuppression is an unavoidable consequence of these therapeutic strategies. Unfortunately, infections during periods of neutropenia are inevitable, and approximately 50% of febrile neutropenia episodes are caused by either established or occult infections (14, 19). The prognosis depends primarily on the duration and depth of neutropenia, with overall mortality rates as high as 11% (4). The management of febrile neutropenia (FN) with a broad-spectrum antibiotic therapy is often used as an empirical strategy (18). The search for the source of the infection is also required, but the reduction of neutrophils in the blood commonly leads to poor symptomatology, and the end-point of biological and radiological investigations may be limited by both insufficient sensitivity and specificity (1, 5, 20).

^{18}F-Fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET) is a functional imaging technique that assesses glucose metabolism following the distribution of a radioactive tracer (^{18}F-FDG). In cases of infection or inflammation, pre-clinical studies using FDG have helped identify elevated glycolysis activity in monocytes, neutrophils and macrophages during their proliferative phase due to a boost in transmembrane glucose transporters and their enhanced affinity for deoxyglucose, which is mediated by growth factors and cytokines (8, 22, 23, 25). In the absence of activation, FDG uptake by immune system cells is low.

^{18}F-FDG-PET is widely used, clinically, for identifying cancerous lesions (15) and has also been used to determine the source of the infection in 165 infectious episodes in patients with multiple myeloma (including patients with chemotherapy-induced FN), as well as to detect infected central venous catheters, deep septic thrombophlebitis and invasive fungal infections(10, 11, 16, 17). Despite the usefulness of this imaging technique, the distinction between an inflammatory tumor (benign or malignant) and infection could be difficult. Limited data are currently available in the literature regarding the application of ^{18}F-FDG-PET in detecting the origin of fever in neutropenic patients with cancer.

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Table I. *Baseline clinical characteristics of the enrolled patients.*

Characteristic	Value	Range
Gender		
Female	22 (46%)	
Male	26 (54%)	
Age (years)		
Median	54	18-76
Mean	49	
Pathology and type of chemotherapy		
AML-induction	28 (58.5%)	
AML-consolidation	4 (8.5%)	
ALL-induction	3 (6%)	
Autologous SCT (NHL, HL, myeloma)	11 (23%)	
Allogeneic SCT (NHL, HL)	2 (4%)	
Neutropenia duration (days)		
Median	15	8-79
Mean	24	
Fever duration (days)		
Median	14	2-51
Mean	16	
Diabetes mellitus (n)	8 (17%)	
Oral diabetic therapy	3 (6%)	
Insulin	5 (10%)	
Concomitant drug		
Corticosteroids	3 (6%)	
Filgrastim/pegfilgrastim	8 (17%)	

AML: Acute myeloblastic leukaemia; ALL: acute lymphoblastic leukaemia; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; SCT: stem cell transplantation.

Table II. *Correlation between conventional evaluation results and fluorodeoxyglucose (FDG) positron-emission tomography uptake.*

		FDG uptake			
	Total no. of patients	Negative	Lung only	Other or multiple sites	*p*-Value
Total	48	24	11	13	
Clinical diagnosis of infection	38	15	11	12	0.016
Pneumonia	17	.	11	6	<0.0001
Typhlitis	13	6	2	5	0.5847
Mucositis	19	13	1	5	0.0438
Other	5	1	.	4	0.0395
Microbiological diagnosis of infection	19	8	5	6	0.6892
Candida albicans	6	3	1	2	1
Aspergillus fumigatus	4	.	3	1	0.0164
Staphylococcus sp. and *Streptococcus sp.*	5	4	.	1	0.4852
Enterococcus faecalis and *Enterobacter sp.*	5	1	1	3	0.165

We designed a monocentric study to investigate the ability of ^{18}F-FDG-PET in finding the foci of infection in hospitalised patients with chemotherapy-induced FN. This study was registered as IDRCB/2006-A00-264-47.

Patients and Methods

Patient selection criteria and data collection. Forty-eight patients were included in the present prospective cohort study. They all suffered from haematological malignancies and had been consecutively diagnosed with chemotherapy-induced persistent FN between 2007 and 2009 at a single Institution (Department of Haematology, Centre Henri Becquerel). The study's principal aim was to assess the ability of ^{18}F-FDG-PET to detect a focus suspected to be the source of infection, in patients with severe neutropenia. The primary outcome of this study was therefore the number of hyper-metabolic foci identified by ^{18}F-FDG-PET in order to establish, as a secondary aim, their concordance with clinical symptoms. The inclusion criteria were as follows: hospitalised patients older than 18 years of age undergoing either high-dose chemotherapy or haematopoietic stem cell transplant (both autologous and allogeneic) to treat underlying haematological malignancy, expected duration of neutropenia longer than seven days, severe neutropenia (absolute neutrophil count <500 cells/μl), and persistent fever (temperature ≥38˚C) for at least 48 h despite conventional broad-spectrum antibiotic therapy (regardless of whether a potential cause of the fever has been identified). Patients who provided written informed consent were enrolled and underwent FDG-PET/CT within five days of enrolment. Exclusion criteria were pregnancy, uncontrolled diabetes (glucose levels greater than 10 mmol/l at the time of ^{18}F-FDG-PET) and haemodynamic instability. Each patient was only included once in this study, even if they presented with a subsequent episode of FN.

Clinical diagnosis of infection was established by the treating physician. Each patient underwent conventional evaluation for FN consisting of a daily complete physical examination by the treating physician, laboratory (daily complete blood count and blood electrolytes, as well as renal and hepatic function tests) and microbiological (peripheral and central venous catheter blood cultures, cytobacteriological urine test, serum galactomannan level monitored twice weekly) testing, standard chest radiography, echography and CT imaging (if clinical abnormalities present suggesting deep tissue infection) and invasive procedures including bronchoalveolar lavage in cases involving respiratory findings (if requested by the treating physician).

Clinical management of FN by the physicians was performed according to local guidelines, including empirical broad-spectrum antibiotic and pre-emptive anti-fungal therapies. Patients with no systemic compromise were treated with intravenous (*i.v.*) piperacillin-tazobactam at 4 g every 8 h as monotherapy, whereas in patients with systemic compromise, *i.v.* amikacin at 15 mg/kg once daily was added. When indicated, *i.v.* vancomycin was administered. This study was approved by the local Committee for the Protection of Persons and by our Institutional scientific and Ethics Committee (approval number IDRCB/2006-A00-264-47) and was conducted in accordance with the Declaration of Helsinki.

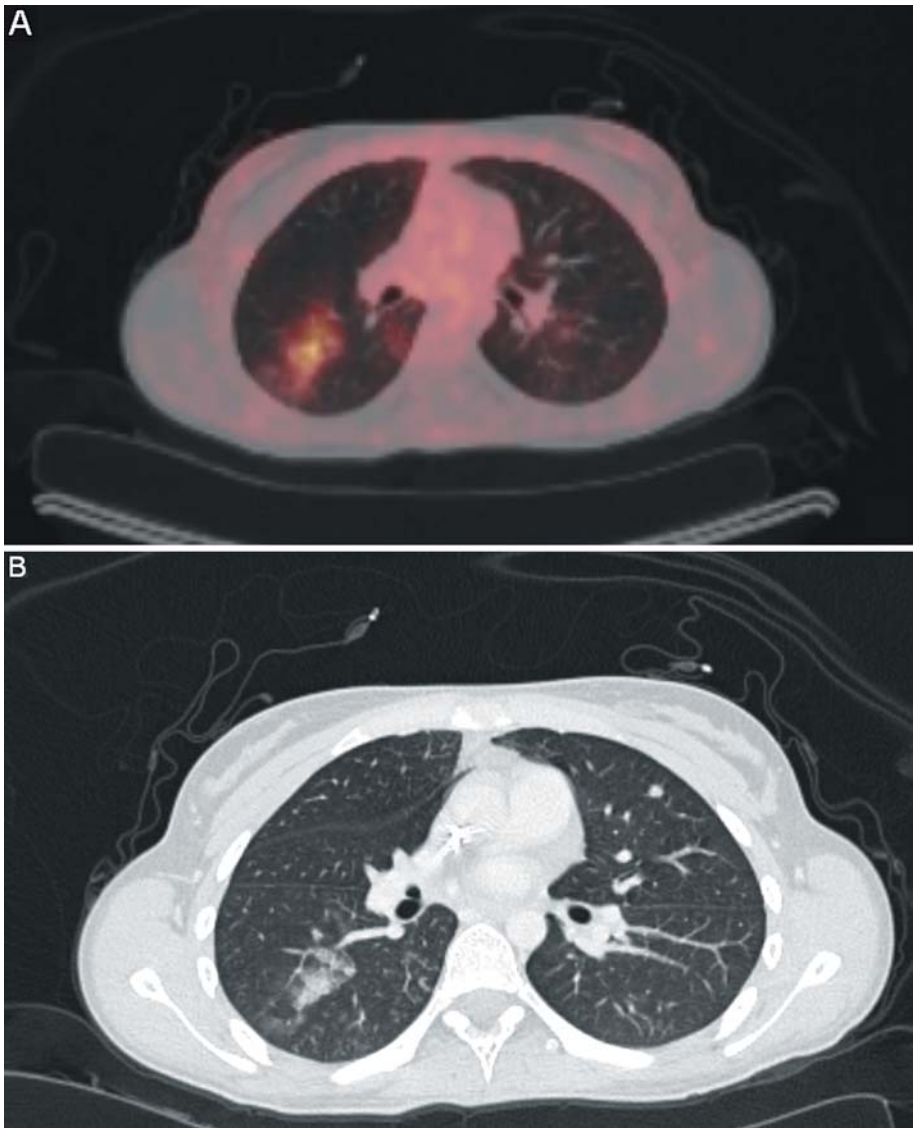

Figure 1. *Fused fluorine-18 fluorodeoxyglucose positron-emission tomography combined with computed tomography image with pathological uptake (A) and computed tomographic scan image (B) suggesting an infectious process in the right lung of a patient.*

^{18}F-FDG-PET/CT. An integrated PET/CT scanner (Biograph LSO Sensation 16, Siemens Medical Solutions, Hoffman Estates IL, 60192, USA) was operated according to the European Association of Nuclear Medicine (EANM) guidelines (2) and used for data acquisition.

Prior to FDG injection, patients had fasted, and *i.v.* infusions containing either glucose or insulin were discontinued for 6 hours. Blood glucose levels were <10 mmol/l at the time of FDG administration. One hour after *i.v.* injection of 5 MBq/kg of FDG (Flucis®; CISBIO international, Gif-sur-Yvette, France), a low-dose CT scan of the area between the proximal femora and the base of the skull was acquired in helical mode at 140 kV and 100 mAs and reconstructed at a slice thickness of 3 mm for anatomical correlation and attenuation correction of the PET data. Subsequently, emission images of the same area were acquired.

FDG-PET/CT was reported as either negative or positive. Negative was defined as either no FDG uptake or FDG uptake related to normal physiological activity. Positive was defined as FDG uptake beyond normal physiological activity, with the pattern of uptake suggestive of infection. Each FDG-PET/CT image was reviewed on a Leonardo multimodality workstation (Siemens Medical Solutions) and interpreted by two nuclear medicine physicians who were provided with the previous results of the clinical evaluation, laboratory testing and conventional imaging. Standard PET/CT included a low-dose non-contrast CT scan performed primarily for anatomical localization and attenuation correction, and was therefore not formally reported. The FDG-PET/CT scan results were made available to the treating physicians immediately upon reporting and aided physicians in conducting

further investigations based on any hypermetabolic foci revealed by the FDG-PET/CT. As the study objective was to assess the ability of FDG-PET/CT to detect infection foci compared to conventional techniques, there was no need to blind the cases.

Statistical analysis. After having described the clinical symptoms, obtained the results of the microbiological analyses and determined foci of FDG uptake, the associations between FDG-PET/CT uptake and clinical, as well as microbiological findings, were examined. More precisely, for each group of clinical symptoms, as well as microbiological findings, its association with FDG uptake was tested using the exact Freeman-Halton test (6). A value of $p<0.05$ was considered to be statistically significant.

Sample size. As the principal outcome was to determine whether FDG-PET/CT is able to identify hypermetabolic foci suspected of being the source of infection, the sample size was determined on the basis of feasibility rather than power considerations. Based on the incidence of persistent FN at our Department of Haematology in the past (approximately 80 patients/year), 48 patients were enrolled in this study.

Results

Forty-eight eligible patients underwent ^{18}F-FDG-PET/CT in addition to clinical evaluation after a minimum of 48 h of persistent FN despite broad-spectrum antibiotic therapy. Table I summarises the selected baseline characteristics of the 48 patients. The median age was 54 years (range=18-79 years), and the majority of patients were males (n=26). The median durations of severe neutropenia (neutrophil count <500 cells/μl) and fever were 15 days (range=8-79 days) and 14 days (range=2-51 days), respectively. Eight patients (17%) presented with controlled diabetes, and eight patients (17%) were treated with either filgrastim or pegfilgrastim in the context of autologous stem cell transplantation. The majority of patients (n=28, 58.5%) presented with acute myeloid leukaemia and were hospitalised for induction chemotherapy.

There were no complications during the acquisition of FDG-PET/CT images from these severely neutropenic patients at the Department of Nuclear Medicine. Pathological FDG uptake identified 31 foci of infections located in the lungs (n=15, 48.4%), colon (n=4, 12.9%), pancreas (n=2, 6.5%), skin (3, 9.7%), ear-nose-throat area (n=5, 16.1%), central venous catheter tract (n=1, 3.2%) and gallbladder (n=1, 3.2%). FDG uptake in these tissue regions was observed in 24 patients (n=50%). Out of these, 11 patients had hypermetabolic foci in the lungs only (Figure 1), whereas 13 patients had multiple foci (n≥2) suspected of being disseminated foci of infection. In two patients, FDG-PET/CT scanning was able to recognise hypermetabolic pancreatic foci, but further investigations (normal serum lipase level, normal abdominal ultrasound and CT scan) excluded the diagnosis of pancreatitis. In addition, one patient had a pathological FDG uptake in the gallbladder, but liver function tests, as well as other imaging techniques (abdominal ultrasound and CT scan), did not find any other evidence of biliary infection. These three cases were considered as probable false-positives.

Clinical evaluation identified 38 patients with four different primary sites of infection (lungs, digestive tract, mucositis, and other sites including the skin and CVC tract, Table II). Clinical evaluation diagnosed 19 patients with mucositis, but FDG uptake was negative for 13 (68.4%) of them. Six patients underwent an abdominal echography, nine patients had a complementary CT of the chest, abdomen and pelvis, and 19 patients had conclusive cultures. The four patients with pathological FDG uptake in the colon had clinical features of infectious colitis or diverticulitis.

Among the 38 patients with a clinical diagnosis of infection, 23 had a pathological FDG uptake, resulting in a FDG-PET/CT sensitivity of 61% (95% Confidence Interval (CI)=43-76%). The prevalence of infections in our study population was 79% and we estimated that the positive predictive value of FDG-PET/CT was 96% (95% CI=79-99.9%). The specificity of FDG-PET/CT was 90% (95% CI=56-99.7%). A diagnosis of infection determined by clinical evaluations was statistically associated with pathological FDG uptake ($p=0.016$). In our study population, clinical respiratory signs suggestive of pneumonia were significantly associated with FDG-PET pathological uptake with lung fixation alone (n=11, $p<0.0001$, Table II). With regard to the microbiological evaluation, positive serum galactomannan levels were significantly associated with pathological FDG-PET uptake ($p=0.0164$), especially with lung fixation alone. For these patients, with lung fixation (n=3), pulmonary aspergillosis was suspected after FDG-PET/CT and this diagnosis was also mentioned after clinical investigations (including CT scan), and proven invasive pulmonary aspergillosis was identified in two out of the three patients.

Discussion

Our study confirmed that limited foci of infection are distinguishable by ^{18}F-FDG-PET/CT in patients with haematological malignancies who have severe chemotherapy-induced neutropenia. Half of the patients in this study had a clearly positive FDG-PET/CT, with no doubt regarding a possible hypermetabolic neoplasm because our patients had acute leukaemia without extramedullary location or lymphoma in complete remission after undergoing autologous/allogeneic stem cell transplantation. These results are in accordance with previously published data estimating that clinically or microbiologically defined infections account for 50% of FN episodes (19). Pathological FDG uptake was observed in 24 patients, even in those with peripheral neutrophil counts lower than 500 cells/μl. It has been demonstrated that FDG-PET/CT can visualize areas of

inflammation due to the accelerated metabolism of activated leucocytes other than neutrophils, such as lymphocytes and macrophages in the tissues (3, 13, 21, 25). FDG passes through the activated leucocyte membrane, and phosphorylated FDG cannot be metabolised by the glycolytic pathway, thus remaining captured inside the cell.

Two preliminary studies with small cohorts (n=28 and n=20) of patients with FN have shown the ability of ^{18}F-FDG-PET/CT scanning to identify localised foci of infection regardless of the absence of circulating neutrophils (9, 24). Our results are consistent with another recently published study establishing that FDG-PET/CT has a potential role in the diagnostic evaluation of patients with persistent FN with a sensitivity and specificity of 79.8% and 32.14%, respectively, compared to 51.7% and 42.85% with chest/sinus CT alone, respectively (7). In the present study involving 79 patients for 91 episodes of persistent FN, FDG-PET/CT resulted in either a change from the pre-test diagnosis or an additional diagnosis in 69% of the episodes, but the specificity was poor due to the positive findings related to either haematological malignancies or inflammatory conditions.

All maximum standardised uptake values in our patients were low, rarely mentioned in the nuclear medicine physicians' reports and did not allow for Receiver Operating Characteristic statistical analysis of the specific diagnostic value of the FDG pathological uptake intensity necessary to identify infections. Receiving filgrastim treatment did not hamper the interpretation of the FDG-PET/CT results in our study. Thirteen patients had negative FDG uptake in case of mucositis but the contribution of any isotopic approach is not expected for this clinical entity.

Our study had several limitations, including the small number of patients, enrolment within a single centre, lack of a control group and incorporation bias with possible overestimation of diagnostic accuracy of FDG-PET/CT; these limitations also existed in earlier studies evaluating the application of FDG-PET/CT to locate infection foci in FN patients (7, 9, 12, 24). In addition, FDG-PET/CT was potentially performed too early after the start of FN and antibiotic therapy, as many patients became febrile shortly after inclusion in our study, which could have led to false-negative FDG uptake. In this situation, it is difficult to associate clinical infection with FDG-PET/CT results. It would be of interest to perform an additional study in which patients are included after a longer minimal duration of fever, as in this study, certain patients were included as early as two days after fever onset.

In our prospective pilot study, the results of the FDG-PET/CT scans did not change the therapeutic attitude or clinical management of the treating physician compared to the clinical evaluation methods. Regarding specificity, FDG-PET/CT identified three hypermetabolic foci of infections that were not confirmed by clinical evaluation (pancreas, gallbladder), and these patients presented no abdominal symptoms. However, we were unable to confirm that these three hypermetabolic foci were false-positive because biopsies were not performed. Indeed, neither biopsies nor colonoscopies were performed to confirm or exclude diagnoses of infection based on FDG-PET/CT results because of the context of severe pancytopenia and the availability of conventional imaging.

In addition, the role of FDG-PET/CT for following a patient's response to anti-infectious therapy remains unclear. Furthermore, there was a small sample size and each patient was only included once in the study. If patients had been included for each separate neutropenic febrile episode, the sample size would have been increased. One particularly interesting finding of this study was the ability of FDG-PET/CT to detect three cases of probable invasive pulmonary aspergillosis. This approach should be pursued to manage this serious infection in neutropenic hosts and there is a need for future studies to evaluate the value of FDG-PET/CT in monitoring the response to antifungal therapy. This approach could enhance the role of PET in the management of invasive pulmonary fungal infection.

Based on the results of this study and previously published data demonstrating the utility of FDG-PET/CT in diagnosing the cause of fever of unknown origin in non-neutropenic patients [17, 18], FDG-PET/CT is now part of our local diagnostic arsenal in the care of patients with FN.

In conclusion, our prospective study demonstrates the ability of FDG-PET/CT to aid in diagnosing infections in severely neutropenic patients with haematological malignancies and two or more days of fever despite empirical broad-spectrum antibiotic therapy. FDG-PET/CT is capable of detecting deep tissue and organ infections, also delineated by conventional diagnostic procedures. In our study, FDG-PET/CT had no advantage over CT scan or conventional evaluation and FDG-PET/CT results did not change the treatment protocol.

Larger multicentre prospective studies are required to better-evaluate the usefulness of FDG-PET/CT in the clinical management of persistent FN and the optimal timing of PET/CT acquisition. We plan to conduct a prospective trial to investigate cases of prolonged FN of more than seven days for which conventional assessments have failed to determine any aetiology.

Conflicts of Interest

The Authors have no competing interests.

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