^{18}F-FDG-PET/CT evaluation of response to treatment in lymphoma: when is the optimal time for the first re-evaluation scan?

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Abstract

Assessing the response to treatment as soon after treatment initiation is one of the key reasons for imaging lymphoma patients. The optimal time after initiating treatment for assessing response to treatment has yet to be determined. Therefore, we were prompted to review our experience with serial ^{18}F-FDG PET/CT in patients undergoing treatment for Hodgkin's disease (HD) and non Hodgkin's lymphoma (NHL). *This is a retrospective study* (Feb 2003 – Oct 2004) *of 20 patients,* 11 men and 9 women, with age range of 7-75 years with diagnosis of HD (10) and NHL (10), who had PET/CT at our institution prior, during and at the completion of therapy. Restaging PET/CT was done after 2 cycles of chemotherapy in 10 patients (group A) and after 4 cycles of chemotherapy in 10 pts (group B). *A total of 60 scans were reviewed.* The ΔSUV from baseline to first PET/CT was on average 67.6% in group A and 75.1% in group B. This had no statistical significance (P value: 0.31). The ΔSUV from baseline to post-therapy PET/CT was on average 72.9% in group A and 79.8% in group B. This difference also had no statistical significance (P value: 0.24). The correlation coefficient was 0.98 in group A and 0.80 in group B. Results of PET/CT after 2 cycles of chemotherapy *did not statistically differ* from the results of PET/CT after 4 cycles of chemotherapy. These results need to be confirmed in larger, prospective, randomized trials.

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Introduction

The American Cancer Society estimated 8,220 new cases of Hodgkin's disease (HD) and 66,120 new cases of non-Hodgkin's lymphoma (NHL) in the United States in 2008. The estimated number of deaths for the same year was 1,350 from HD and 19,160 from NHL [1]. Assessing the response to treatment as soon after treatment initiation is one of the key reasons for imaging lymphoma patients and fluoro-18 fluorodeoxy d-glycose (^{18}F-FDG) positron emission tomography and computed tomography (PET/CT) is an essential tool.

Combined ^{18}F-FDG PET/CT scanners are becoming widely available as a powerful non-invasive imaging modality, combining the ability to detect active glucose metabolic processes and their morphologic features in a single study. The role of ^{18}F-FDG PET/CT is relatively well proven in lymphoma, melanoma, colorectal carcinoma, and other cancers [2, 3]. The optimal time after initiating treatment for assessing response to treatment in lymphoma has yet to be clearly determined. Therefore, we were prompted to review our experience with serial ^{18}F-FDG PET/CT in patients undergoing treatment for HD and NHL.

Materials and methods

This is a retrospective study (Feb 2003 – Oct 2004) of 20 patients with histological diagnosis of HD (10) and NHL (10), who each had three ^{18}F-FDG PET/CT scans at our institution prior, during and at the completion of treatment. Treatment consisted of Stanford V (combination of mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone followed by radiation therapy) for HD and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) for NHL. The group included 11 men and 9 women, with age range of 7-75 years (average: 39.6±23.8). The administered doses of ^{18}F-FDG ranged 270-710 MBq (average: 544±88,8 MBq). The first restaging PET/CT was done after 2 cycles of chemotherapy (average: 134±42.9 days) in 10 patients (group A, 5 HD and 5 NHL) and after 4 cycles of chemotherapy (average: 166±66 days) in another 10

patients (group B, 5 HD and 5 NHL). The assessment of response to therapy was based on the European Organisation for Research and Treatment of Cancer (EORTC) criteria for PET [4]. Blinded re-interpretation of the imaging studies by two Nuclear Medicine physicians (AI, AQ) for accuracy and data analysis from medical records were performed. Percentage changes (Δ) from baseline in the sum of maximum standardized uptake value (SUVmax) in up to five lesions with highest SUVmax values and percentage changes in size of these lesions, were calculated for the follow-up PET/CT scans.

The study was performed with approval of the Institutional Review Board. The inclusion criteria were histopathologically proven diagnosis of lymphoma and availability of baseline, mid-treatment and post-treatment PET/CT scans for review. The reports of PET/CT scans and pathology examinations were reviewed and their results were recorded.

The ^{18}F-FDG PET/CT scans were acquired using a Discovery LS PET/CT unit (GE Medical Systems, Milwaukee, WI). The patients fasted at least 6 h prior to imaging and their blood glucose levels were less than 150 mg/dl at the time of the tracer injection. Approximately 60 min after tracer administration, a CT scan (5 mm contiguous axial cuts) was obtained in four integrated multi-slice helical non contrast CT, from top of the head to mid thighs. The acquisition was obtained in helical mode, using 140 kV, 40 mAs and a 512x512 matrix size, acquiring a field of view (FOV) of 867 mm in 22.5 s. This CT- based scan was used for attenuation correction purposes and to help in anatomic localization of ^{18}F-FDG. Immediately after the CT, an emission PET scan was acquired in 2D mode over the same anatomical regions starting at the level of the thighs for molecular/metabolic information. The acquisition time was 5 min per bed position (35 slices/bed) in 6 beds, with a one-slice overlap at the borders of the FOV. The PET emission scan was corrected using segmented attenuation data of the conventional transmission scan. The PET images were reconstructed with a standard iterative algorithm (OSEM, two iterative steps, 28 subsets) using GE software release 5.0. All images were reformatted into axial, coronal, and sagittal views and viewed with the software provided by the manufacturer (Entegra version 1.123, GE Medical Systems, Haifa, Israel).

Semi-quantitative analysis of the ^{18}F-FDG uptake in the suspected lesions was based on calculation of SUV, defined as the ratio of activity per milliliter of tissue to the activity in the injected dose corrected by decay and per patient's body weight. Accuracy is greater than 3 significant digits for maximum SUV (SUVmax) value [5]. Regions of interest were placed around the regions of increased ^{18}F-FDG uptake for SUVmax determination.

Confidence interval (CI) estimations were performed using the Wilson score method [6]. Correlation analysis of ΔSUV between re-staging scans for groups A and B was conducted using the mean deviation method. ANOVA (two-factor with replication) was used for analysis of the 2 groups.

Results

A total of 60 PET/CT scans were reviewed. The ΔSUV from baseline to first PET/CT ranged 3.2%-92.3% (average: 67.6%±26.3%) in group A and 46.6%-89.6% (average: 75.1%±13.3%) in group B. This difference between groups A and B has no statistical significance (*P* value: 0.31; *F*<*F* critical). The ΔSUV from baseline to post- treatment PET/CT ranged 11.9%-94.4% (average: 72.9%±22.8%) in group A and 53.4%-89.9% (average: 79.8%±10.3%) in group B. This difference also had no statistical significance (*P* value: 0.24; *F*<*F* critical). These results are presented in Figure 1. The correlation coefficient was 0.98 in group A and 0.80 in group B, as seen in Figure 2.

There were 2 deaths and 1 relapse in group A (at 7, 14 and 9 months, respectively) and 1 death and 1 relapse in group B (at 8 and 15 months, respectively). The patients in remission were followed-up clinically for 14-32 months (average: 22±5.2).

The subject presented in Figure 3 is a 75-year-old man with NHL. Pre-treatment ^{18}F-FDG PET/CT showed extensive abdominal disease. PET/CT after 2 cycles of chemotherapy indicated partial metabolic response to R-CHOP treatment. At the end of treatment the scan remained positive. A 19-year-old man with HD is shown in Figure 4. Pre-treatment ^{18}F-FDG PET/CT indicated extensive disease involvement. PET/CT after 4 cycles of chemotherapy showed complete metabolic response to Stanford V treatment. The scan at the end of treatment remained negative. Figure 5 presents a 66-year-old man with NHL. Pre-treatment ^{18}F-FDG PET/CT showed abdominal disease. PET/CT after 4 cycles of chemotherapy indicated partial metabolic response to R-CHOP therapy. At the end of the treatment the scan was negative.

Discussion

^{18}F-FDG PET and PET/CT is at least equivalent to CT for the initial staging of lymphomas [7]. However, the impact of combined PET/CT and fast-scanning CT with contrast has yet to be evaluated in the management of lymphoma patients. At this point, ^{18}F-FDG PET and CT must be considered as giving complementary staging information. ^{18}F-FDG PET also has high diagnostic accuracy for restaging lymphoma after initial treatment [7, 8]. ^{18}F-FDG PET has shown high accuracy in the early prediction of response to chemotherapy and in the evaluation of residual masses after chemotherapy or radiation therapy [9]. Therefore, PET is likely to play a major role in tailoring the intensity of the treatment to the individual patient. A pre-treatment PET study is essential for accurate assessment of residual masses and early monitoring of response to the treatment. In addition, a baseline PET scan will help detect relapse or residual disease, because relapse occurs most often in the region of previous disease.

^{18}F-FDG PET is regarded as a superior modality, compared to CT, for assessing post-treatment response in lymphoma patients [10, 11]. Its superiority lies in its ability to dif-

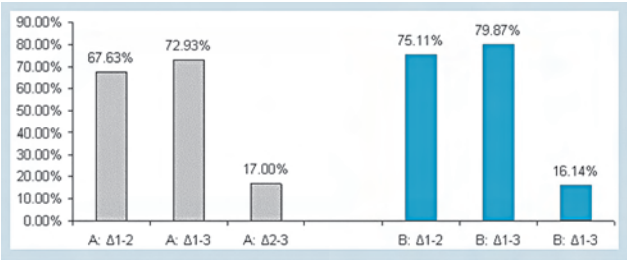

Figure 1. Percent changes in ΔSUV from baseline to first and second re-evaluation scans in groups A and B.

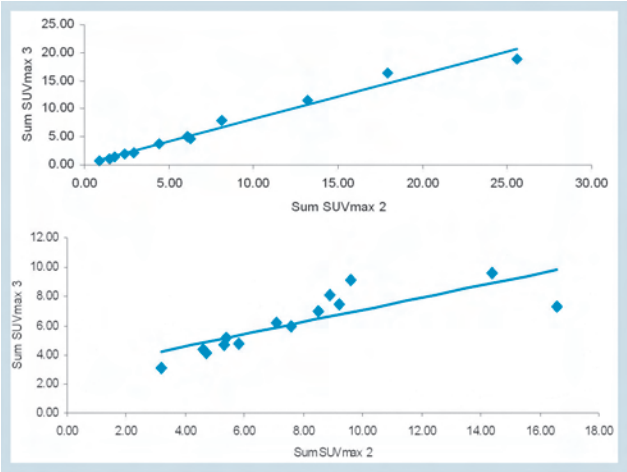

Figure 2. Correlation analysis of SUVmax values at first and second re-evaluation scans in patients from group A and B.

ferentiate viable tumor from fibrosis. This is important since up to 64% of patients with HD will present with a residual mass on CT following treatment, but only 18% will actually relapse [12].

It is desirable to assess response and predict prognosis as early as possible after treatment begins. Mid-treatment ^{18}F-FDG PET scans have already been shown to be useful for early prediction of treatment response in both NHL and HD [13-16]. So far, Mikhaeel et al. (2005) has provided the largest study on this subject. They included 121 patients with aggressive NHL and showed that ^{18}F-FDG PET scans after 2-3 cycles of chemotherapy can predict progression-free and overall survival [14]. Kostakoglu et al. (2002) showed that interim ^{18}F-FDG PET scans may be able to predict response as early as after 1 cycle of treatment [16]. Currently, the optimal timing of the interim ^{18}F-FDG PET remains unclear as the predictive values of ^{18}F-FDG-PET scans obtained at different mid-treatment periods have not been compared within a single study. Our retrospective study attempted to determine if there are any statistical differences between mid-treatment ^{18}F-FDG PET/CT scans obtained after 2 and 4 cycles in predicting post-treatment response.

Our results show that both ^{18}F-FDG PET/CT scans obtained at 2 and 4 cycles correlated well (correlation coefficient 0.98 and 0.80, respectively) with end-treatment response. Furthermore, scans performed at 2 cycles did not differ significantly from scans performed at 4 cycles in terms of ΔSUV

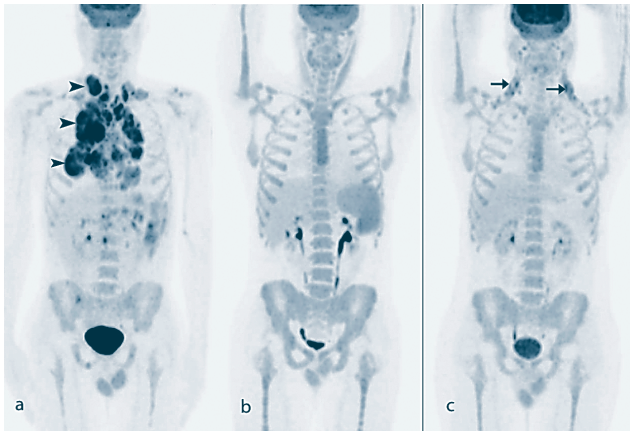

Figure 3. A seventy five years old man with NHL. a) Pre-treatment FDG PET/CT showed extensive abdominal disease (arrowheads); b) PET/CT after 2 cycles of chemotherapy indicated partial metabolic response to R-CHOP treatment; c) at the end of therapy the scan remained positive (arrowheads).

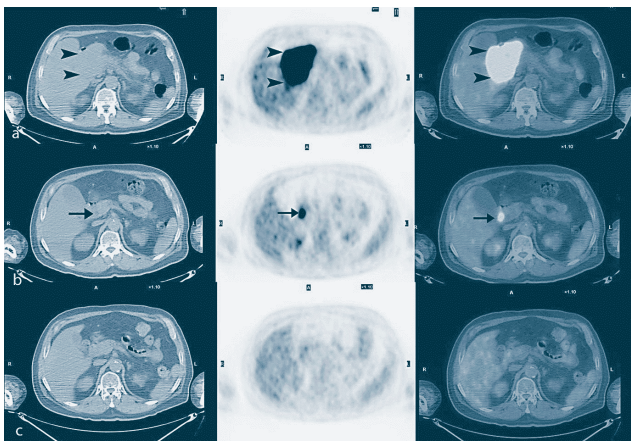

Figure 4. A nineteen years old man with HD. a) Pre-treatment 18F-FDG PET/CT indicated extensive disease involvement (arrowheads); b) PET/CT after 4 cycles of chemotherapy showed complete metabolic response to Stanford V treatment; c) the scan at the end of treatment remained negative, with bilateral neck 18F-FDG uptake in metabolically active brown fat (arrows).

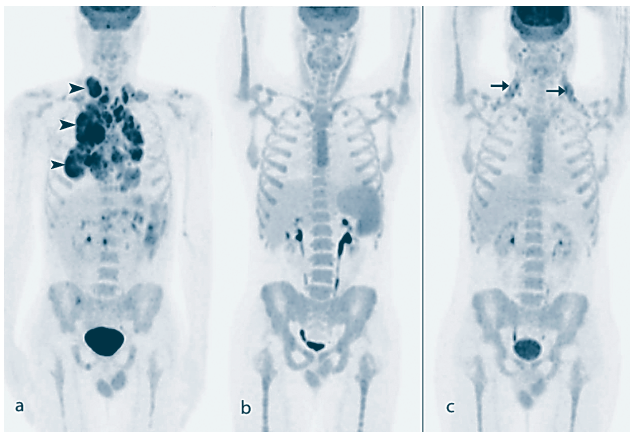

Figure 5. Transaxial CT (left), PET (middle) and fused PET/CT (right) of a 66 years old man with NHL. a) pre-treatment images showed abdominal disease (arrowheads); b) images after 4 cycles of chemotherapy indicated partial metabolic response to R-CHOP therapy (arrows); c) at the end of the treatment the scan was negative.

from baseline to post-treatment. This implies that patients who fail to respond to treatment can be identified by ^{18}F-FDG PET as early as after 2 cycles, and that these patents can be spared additional cycles of an ineffective treatment and be switched to an alternative chemotherapy regimen. Conversely, patients who respond after 2 cycles should complete the full course of chemotherapy as they will likely have an excellent prognosis.

A limitation of this study is the small number of patients, which may decrease our ability to detect statistical differences. We also included both NHL and HD patients, who respond differently to therapy and were treated with different regimens. Less than 50% of patients with aggressive NHL respond to induction chemotherapy, whereas HL patients have a much high response rate and have better overall prognosis [17]. Including both types of lymphoma in this study has the potential to bias the results toward higher concurrence between mid-treatment and post-treatment results. But this bias applies to mid-treatment scans performed at both 1-2 and 3-4 weeks, so it should not marginalize our findings, which focus on detecting differences between scans performed at different mid-treatment periods.

In conclusion, our study suggests that in this patient population, with these treatment regimens, the results of PET/CT after 2 cycles of chemotherapy did not statistically differ from the results of PET/CT after 4 cycles of chemotherapy. The first restaging PET/CT (whether after 2 or 4 cycles of chemotherapy) allows an accurate estimation of the response to treatment, without statistically significant changes in comparison to the PET/CT results at the completion of treatment. These results need to be confirmed in a larger, prospective trial or more likely through combining multiple retrospective trials from different institutions.

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