Persistent tumor \(^{18}\)F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma

GUY JERUSALEM,* YVES BEGUIN,* MARIE-FRANCE FASSOTTE,* FADI NAJJAR,° PATRICK PAULUS,° PIERRE RIGO,° GEORGES FILLET*

Department of Medicine, Divisions of *Onco-Hematology and °Nuclear Medicine, University of Liège, Liège, Belgium

**ABSTRACT**

Persistent tumor \(^{18}\)F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma (NHL).

**Design and Methods.** We studied 28 patients by \(^{18}\)F-FDG PET after a median of 3 cycles of polychemotherapy. The presence or absence of abnormal \(^{18}\)F-FDG uptake was correlated to clinical outcome (median follow-up: 17.5 months, range 4.47 months).

**Results.** Five of 28 patients still had increased \(^{18}\)F-FDG uptake in one or more sites previously shown to be involved by lymphoma at baseline evaluation. Only one of these five patients entered complete remission (CR), whereas among the 23 patients with negative \(^{18}\)F-FDG PET studies, two died of toxicity during chemotherapy and all the others entered clinical CR (p=0.00001). All five patients with and 7/21 patients without residual abnormal \(^{18}\)F-FDG uptake relapsed or reprogressed (positive predictive value for relapse: 100%, negative predictive value: 67%). By Kaplan-Meier analysis, progression-free survival (PFS) at 1 and 2 years was respectively 20±18% and 0% for \(^{18}\)F-FDG PET positive patients and 81±9% and 62±12% for \(^{18}\)F-FDG PET negative patients (p=0.0001). Overall survival (OS) at 1 and 2 years was respectively 20±18% and 0% for \(^{18}\)F-FDG PET positive and 87±7% and 68±11% for \(^{18}\)F-FDG PET negative patients (p=0.0001).

**Interpretation and Conclusions.** Persistent tumoral \(^{18}\)F-FDG uptake after a few cycles of polychemotherapy is predictive of CR, PFS and OS in NHL. Further studies are warranted to determine whether \(^{18}\)F-FDG PET has a predictive value independent from conventional prognostic factors. However, the sensitivity of qualitative \(^{18}\)F-FDG PET imaging in identifying patients with a poor outcome was insufficient. Earlier evaluation after only one cycle of chemotherapy and quantitative analysis might increase the sensitivity of \(^{18}\)F-FDG PET is predicting treatment failure.

©2000, Ferrata Storti Foundation
were also evaluated by 18F-FDG PET at diagnosis; the other 3 were not because the PET scan was not available rapidly enough.

Early treatment evaluation

Early evaluation by 18F-FDG PET was scheduled to be performed after 2-3 cycles of polychemotherapy. However, this was not possible in all of them for various reasons (infectious or other complications, technical reasons). Therefore, 11 patients were studied after 2 cycles, 10 after 3 cycles, 6 after 4 cycles and 1 after 5 cycles. Complete resting with conventional imaging was not done at this time but 18F-FDG PET images were correlated with baseline clinical and CT examination. Comparison with baseline 18F-FDG PET was realized in all 25 available cases.

End of treatment evaluation

One or two months after completion of therapy (median 6 (range 4-10) cycles of chemotherapy), all patients were re-evaluated by clinical examination and computed tomography with intravenous contrast enhancement to determine whether they had achieved CR. In the case of residual masses, a clinical CR was defined by stable masses during further follow-up of at least six months.

18F-FDG PET studies

Whole-body PET using 18F-FDG was performed with a Penn Pet 240-H Scanner (UGM, Philadelphia, PA, USA). Emission scans were recorded 45-90 min after intravenous administration of 200-300 MBq of 18F-FDG. All patients were asked to fast for at least 6 hours prior to the study. A whole-body acquisition was performed from the cervical to the inguinal region. This consisted of 10-12 separate overlapping acquisitions each covering 12.8 cm and performed over 4 minutes. Each subsequent acquisition was performed after a 6.4 cm displacement of the table. The total time of image acquisition was about 50 minutes. Images were reconstructed using filtered back projection with a Hanning filter and were reoriented in transverse, coronal and sagittal planes. A 4 mm voxel size was used. Isotropic 3D resolution was better than 8 mm. PET interpretation was performed in a qualitative manner without attenuation correction. All PET images were analyzed by a physician in the division of nuclear medicine and then reviewed by one investigator (GJ). Any focus of increased 18F-FDG uptake over background not located in areas of normal 18F-FDG uptake (central nervous system, heart, digestive tract, thyroid, muscles) and/or excretion (urinary tract) was considered positive for tumor.

Furosemide (20 mg in slow intravenous injection) was administered in patients with suspected pelvic abnormalities to enhance 18F-FDG urinary elimination. These patients were studied later (60-90 minutes) and after voiding. Diazepam (5 mg) was given orally before 18F-FDG administration in most patients to prevent muscular uptake.

Statistical methods

Comparison of groups for the probability of CR was performed with Yates’ corrected chi-squared tests. OS and PFS were determined by standard Kaplan-Meier survival analysis, and comparison between groups was done by the log-rank test. All analyses were performed using Graphpad Prism 2.01 (Graphpad Software, San Diego, CA, USA).

Results

Five of 28 patients still had increased 18F-FDG uptake in one or more sites previously shown to be involved by lymphoma at diagnosis (Table 2). Three of these 5 patients were studied after 2 cycles, one after 3 cycles and one after 5 cycles. One patient was studied at frontline therapy, two at first relapse and two at transformation from low-grade lymphoma. The patient in frontline treatment entered CR but relapsed 16 months after diagnosis and died a few weeks later. The other 4 patients never achieved CR, reprogressing 3, 3, 5 and 9 months after the start of polychemotherapy and dying 2, 2, 3 and 2 months later, respectively.

After a few courses of polychemotherapy 18F-FDG PET was negative in 23/28 patients. All patients

Table 1. Patient characteristics.

| Number of cases | 28 |
| Age (years) | 61 |
| (range 23-80 years) |
| Sex |
| Male | 14 |
| Female | 14 |
| Histology (REAL Classification) |
| Follicle center lymphoma, follicular, grade II | 3 |
| Follicle center lymphoma, follicular, grade III | 3 |
| Follicle center lymphoma, diffuse, small cell | 3 |
| Diffuse large B cell lymphoma | 16 |
| Peripheral T cell lymphoma, unspecified | 2 |
| Precursor T lymphoblastic lymphoma | 1 |
| Disease status |
| Frontline therapy | 23 |
| First relapse | 3 |
| Transformed from low-grade lymphoma | 2 |
| Ann Arbor clinical stage |
| Stage I | 4 |
| Stage II | 4 |
| Stage III | 5 |
| Stage IV | 15 |
| Treatment |
| Anthracycline-based polychemotherapy | 23 |
| Mitoxantrone-based polychemotherapy | 2 |
| Cisplatin-based polychemotherapy | 3 |

Table 2: Sites of abnormal 18F-FDG uptake in 5 patients.

1. Lung, pleura
2. Lymph nodes (medialstinal, retroperitoneal), bone (humerus)
3. Lymph nodes (abdominal mass)
4. Lymph nodes (medialstinal)
5. Lymph nodes (medialstinal, lung)
except one (in first relapse) were studied at frontline therapy. Two patients died of toxicity during chemotherapy. The other 21 patients entered clinical CR. Fourteen of these 21 patients remained in CR after a median follow-up of 28 months (range: 10-47 months) from diagnosis. Seven patients relapsed after a median follow-up of 10 months (range: 4-22 months). Five of these 7 patients died 11-23 months (median 15 months) after diagnosis and 2 are alive with disease 13 and 46 months after diagnosis.

The probability of achieving CR (20% vs 100%, \(p<0.00001\)) was significantly lower in patients with positive 18F-FDG PET after a few cycles of polychemotherapy. OS (20±18% vs 87±7% at 1 year, 0% vs 68±11% at 2 years, \(p<0.0001\)) and PFS (20±18% vs 81±9% at 1 year, 0% vs 62±12% at 2 years, \(p=0.0001\)) were also significantly different between the two groups. An example of a positive 18F-FDG PET study before and negative 18F-FDG PET study after 3 cycles of chemotherapy is illustrated in Figure 3.

Discussion

Armitage et al. have shown that CR, as assessed by plain films and computerized tomography scans, can be achieved in 70% of patients during the first 3 cycles of treatment. The length of time to reach CR was predictive of outcome. Sixty percent of those who did not achieve CR before cycle 5 of chemotherapy relapsed within 2 years. When CR was achieved after only 3 cycles, the relapse rate was only 20%. However, time to reach CR may be an imperfect indicator of the quality of response since the degree of tumor reduction differs between patients according to the size of initial masses, their site, histology and the type of treatment. In addition, differentiation of tumor from fibrosis within residual radiographic masses is a problem in the differential diagnosis of residual disease in lymphoma.

\(^{67}\)Ga imaging has been shown to be very useful in the monitoring of disease response or detection of recurrence in lymphoma. In a retrospective study, Kaplan et al. reported that persistent \(^{67}\)Ga uptake after four to six cycles of combination chemotherapy for diffuse large cell lymphoma predicted a poor outcome. Patients with negative \(^{67}\)Ga scans had a 70% disease-free survival (DFS) at 3 years, whereas patients with positive scans had only a 24% DFS. Jancicke et al. prospectively evaluated 30 poor prognosis patients (bulky disease \(\geq\) 10 cm, advanced stage aggressive NHL) with chest/abdominal/pelvic CT scans and \(^{67}\)Ga scans at baseline and following two cycles of therapy. After a median follow-up of 31 months, 94% of patients who had negative early restaging \(^{67}\)Ga scans (18/19 patients) remained free from progression, versus only 18% of those with positive scans (2/11). Preliminary results by Fayad et al. indicated that a positive \(^{67}\)Ga scan after 2 cycles identified a subgroup of patients with aggressive NHL with poor outcome independently of tumor score. Three-year PFS and OS were respectively 53% and 65% for \(^{67}\)Ga-negative (n=70) and 29% and 40% for \(^{67}\)Ga-positive (n=31) patients. Preliminary results by Ben-Haim et al. also showed that \(^{67}\)Ga scan after one course of chemotherapy reliably predicted response to therapy in lymphoma patients. Twenty of the 22 patients (91%) with a negative \(^{67}\)Ga scan and 12 of the 23 patients (52%) with a positive \(^{67}\)Ga scan achieved CR. Fourteen \(^{67}\)Ga-positive and 7 \(^{67}\)Ga-negative patients relapsed and DFS was significantly different.

Despite the important role of \(^{67}\)Ga in lymphoma imaging, 18F-FDG PET may be a more effective agent. 18F-FDG PET scanning is likely to be favored by clinicians and patients alike, because it allows same day imaging and because of the inherent superiority of PET imaging methods over standard gamma camera imaging in terms of sensitivity and spatial resolution. PET is also superior to conventional staging in this setting. Newman et al. showed in a pilot study includ-
ing 16 patients that 18F-FDG PET is more accurate than CT in the nodal staging of lymphoma patients. A confirmatory study including 27 patients with Hodgkin’s disease and 33 patients with NHL was reported by Moog et al. PET showed lymphomatous involvement in 25 additional sites compared to those shown by CT (7 true positives, 2 false negatives, 16 unresolved). CT also showed some additional regions involved compared to those revealed by PET (3 false-positives, 3 unresolved). Staging was changed due to PET in 4 patients. 18F-FDG PET imaging may also provide more information than CT for the detection of extranodal lymphoma. In addition, 18F-FDG PET could also detect bone marrow involvement not shown by bone marrow biopsy.

Hoekstra et al. compared results of early evaluation of response to treatment by 67Ga scintigraphy or by planar 18F-FDG scintigraphy with a conventional gamma-camera and a special collimator in 26 patients (13 with Hodgkin’s disease (HD) and 13 with NHL). The scintigraphic appearance of involved sites was essentially the same with both tracers. In patients eventually achieving CR, tracer distribution had normalized after two courses; high uptake reflected treatment failure; faint uptake was associated with variable outcome. For investigation of residual masses and pre-treatment staging 67Ga was the preferred tracer because of higher contrast. However, in areas with considerable physiological 67Ga uptake, planar 18F-FDG scintigraphy could provide complementary information. Dimitrakopoulou-Strauss et al. studied 10 patients with HD and NHL in relapse by 18F-FDG PET. They showed that a decrease in 18F-FDG uptake was associated with successful response to therapy, while progressive disease was correlated with increasing 18F-FDG uptake. Römer et al. reported in their quantitative 18F-FDG PET study that standard chemotherapy of patients with NHL caused a rapid decrease of tumor 18F-FDG uptake as early as 7 days after treatment. The mean metabolic rates for 18F-FDG 7 days after initiation of chemotherapy was significantly lower in the 6 of 11 patients still in CR after a follow-up of 16±4 months. However, 18F-FDG uptake at 42 days was better than day 7 parameters in predicting long-term outcome.

Our study confirmed the prognostic value of early disease evaluation by 18F-FDG PET. The results in NHL patients showed that persistent tumor 18F-FDG uptake after 2-5 cycles of polychemotherapy was highly predictive of outcome, including the probability of achieving CR, PFS and OS. Only 1 of 5 patients entered CR but relapsed later. The positive predictive value of 18F-FDG PET after 2-5 cycles of polychemotherapy (defined as true positive by relapse and/or positive biopsy) was thus 100% (5/5) with no false positives. We did not attempt to correlate the results of positive 18F-FDG PET with conventional imaging techniques in this study. Early treatment evaluation by CT is disappointing because residual masses do not necessarily represent residual tumors. We previously reported that 18F-FDG PET has higher diagnostic and prognostic value than classical CT scan imaging at the end of treatment evaluation in patients with HD or NHL. Zinzani et al. recently confirmed our findings in lymphoma patients with abdominal masses who have positive CT scans at restaging. PET should be considered the noninvasive imaging modality of choice for differentiating early recurrences or residual disease from fibrosis.

Pre-treatment 18F-FDG PET studies are useful to confirm that later residual 18F-FDG uptake is localized in areas involved by lymphoma at diagnosis. However, in routine clinical circumstances, the same information is already provided by the results of CT and clin-
ical examination at diagnosis. If residual 18F-FDG uptake is localized outside of known involved areas, inflammatory lesions must be excluded.

Qualitative 18F-FDG PET studies were not influenced by time between injection and imaging, as already reported in our previous study of NHL staging at diagnosis. However, the time after injection is an important variable for quantitative PET studies. Significant differences in standard uptake values (SUV) might be found in a single tumor during a single scanning session depending on where in the body and, hence, when in the scanning sequence, the tumor is visualized.

Our patient population was relatively heterogeneous. We could not analyze patients treated by first line anthracyclin-based chemotherapy separately because only one of them had persisting 18F-FDG uptake. Most patients who had persistent 18F-FDG uptake were at high risk of treatment failure (2 patients in first relapse, 2 patients with transformed high-grade NHL). The true predictive value of 18F-FDG PET should be confirmed in a more homogeneous patient population treated with the same chemotherapy regimen.

On the other hand, a negative 18F-FDG PET study after 2-4 cycles of chemotherapy confers a good probability of CR at the end of treatment (100% in our study). However relapses can still occur, even if 18F-FDG PET studies are negative. The negative predictive value (defined as true negative by the absence of relapse and/or negative biopsy of residual masses) was only 67% (14/21). Seven of 21 patients without residual abnormal 18F-FDG uptake relapsed or regressed. Thus, the sensitivity to identify poor outcome remains suboptimal. Earlier evaluation by 18F-FDG PET might be useful to recognize slower responders but this remains to be demonstrated. With our qualitative evaluation, low uptake is difficult to distinguish from background. Therefore, only quantification of 18F-FDG uptake with attenuation correction would allow more sensitive and earlier response evaluation than in our study. Major alterations of 18F-FDG uptake are easily recognized within days after starting chemotherapy and therapy-induced changes in 18F-FDG uptake might thus predict therapeutic efficacy.

Early identification of non-responders by 18F-FDG PET may lead in the future to a change from an unsuccessful therapy to a more effective one. Patients whose tumors remain 18F-FDG PET positive in the course of chemotherapy could be candidates for alternative treatment such as high-dose chemotherapy with autologous stem cell transplantation. However, only a large randomized trial will be able to determine whether such an approach could change the outcome of these patients.

In conclusion, our study demonstrates that persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of CR, PFS and OS in NHL. Most of the patients with persistent tumor 18F-FDG uptake did not achieve CR. A negative 18F-FDG PET study after 2-4 cycles of polychemotherapy confers a good probability of long-term survival but relapses can still occur. A positive 18F-FDG PET scan predicts lack of response rather than relapse. Earlier evaluation after only one cycle of chemotherapy and quantitative analysis might increase the sensitivity of 18F-FDG PET to predict relapse. Further studies are warranted to determine whether 18F-FDG PET has predictive value independently of conventional prognostic factors.

Potential implications for clinical practice

• Early identification of non-responders to chemotherapy is possible by 18F-FDG PET
• A good probability of long-term survival is only observed in patients with negative 18F-FDG PET
• Relapses can still occur, even if 18F-FDG PET studies are negative.
• Further studies are warranted to determine whether 18F-FDG PET has predictive value independently of conventional prognostic factors.

Contributions and Acknowledgments

We declare that all authors participated actively in the design, execution, analysis and writing of the study. GJ, YB, MF Fassotte and GF were involved in the clinical diagnosis and treatment of patients and in the collection of clinical data. YB performed the statistical analysis. FN, PP and PR were involved in all practical aspects of nuclear medicine from image acquisition to interpretation. All seven authors actively participated in correlating clinical and imaging data. They approved the content of the revised manuscript. They accepted the order of authorship. The order of authorship is related to the importance of their contribution to the analysis, writing up and revision of the manuscript.

Funding

Y Beguin is Research Director of the National Fund for Scientific Research, Belgium.

Disclosures

Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received December 27, 1999; accepted March 6, 2000.

References

5. Gallagher BM, Fowler JS, Gutierrez NJ, MacGregor RR, Wan CN, Wolf AP. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of (F-18)-2-deoxy-


