Evaluation of response to fractionated radioimmunotherapy with ^{90}Y-epratuzumab in non-Hodgkin's lymphoma by ^{18}F-fluorodeoxyglucose positron emission tomography

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ABSTRACT

Background
The study aimed to evaluate FDG-PET imaging for early prediction of response to radioimmunotherapy in patients with non-Hodgkin's lymphoma.

Design and Methods
Twenty-seven patients from a large ongoing, multicenter, phase I/II trial of fractionated radioimmunotherapy using anti-CD22 ^{90}Y-epratuzumab underwent FDG-PET imaging. They also underwent assessment by conventional diagnostic methods that included chemotherapy at baseline and six weeks post-radioimmunotherapy, and every three months until progression. Responses evaluated from conventional methods were classified using International Workshop Response Criteria as complete response, unconfirmed CR, partial response, stable disease, or progression of disease. FDG-PET images were evaluated visually and were classified as complete response, partial response or progression of disease. The gold standard was histology and follow-up.

Results
A total of 81 paired imaging studies were obtained post-radioimmunotherapy (including 3 patients after retreatment) and evaluated as complete response (n=34), partial response (n=24) or progression of disease (n=23) by FDG-PET, and complete response (n=12), unconfirmed complete response (n=31), partial response (n=15), stable disease (n=8) or progression of disease (n=15) by conventional methods. Of the 31 responses evaluated as unconfirmed complete response by conventional methods, 20 (65%) were classified as negative for disease (complete response) by PET while the other 11 (35%) were positive for disease (7 partial response and 4 progression of disease). Among 22 assessable PET images acquired at six weeks post-radioimmunotherapy, the mean time-to-progression was 15.6 months when PET was negative for disease (complete response), compared with 5.4 months when PET was positive (partial response or progression of disease) (p=0.008). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET six weeks after radioimmunotherapy were 86%, 63%, 80%, 71% and 77% respectively, compared with 36%, 87%, 83%, 44% and 55% respectively using conventional methods.

Conclusions
A positive assessment of disease by PET acquired six weeks after radioimmunotherapy corresponded with a shorter time to progression.

Key words: CD22, FDG-PET, non-Hodgkin's lymphoma, radioimmunotherapy, tumor response.

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Introduction

Radioimmunotherapy is a new method of targeted therapy in which radiation from radionuclides is delivered more selectively to the tumor by using antibodies directed to tumor-associated antigens.[1] Today, radioimmunotherapy can be used in clinical practice with non-ablative radioactivity of murine anti-CD20 ^{131}I-tositumomab (Bexxar®, GlaxoSmithKline, Philadelphia, PA, USA) approved in the United States, and with ^{90}Y-ibritumomab tiuxetan (Zevalin™, Biogen IDEC Pharmaceuticals, San Diego, CA, USA) approved in Europe and in the United States for treatment of patients with relapsed or refractory follicular lymphoma (FL).[2-6] Other antibodies, such as the humanized anti-CD22 ^{90}Y-epratuzumab, are undergoing clinical development.[7-12] ^{90}Y-epratuzumab is humanized, internalized by target cells, stably-labeled using DOTA, and administered without a loading dose of cold antibody, in contrast to Zevalin® or Bexxar®. These characteristics make it sutable for use in radioimmunotherapy. Indeed, humanization allows fractionated injections, and a single-center study demonstrated the feasibility of repeated injections due to the low immunogenicity of epratuzumab.[11]

Positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) has been successfully evaluated in the management of non-Hodgkin's (NHL) and Hodgkin's lymphoma (HL).[13-20] The most recent international guidelines, formulated in an International Harmonization Project (IHP), recommended FDG-PET or FDG-PET/CT for initial staging and final therapeutic assessment of lymphoma when the end-point is complete response rate.[21-23] FDG-PET after completion of therapy should be performed at least three weeks, and preferably six to eight weeks, after chemotherapy or chemoimmunotherapy, and eight to 12 weeks after radiation or chemoradiotherapy.[21] FDG-PET should only be used for treatment monitoring during a course of therapy in clinical trials or as part of a prospective registry. Nevertheless, several studies have suggested the benefit of FDG-PET for early chemotherapy assessment.[16-19]

Radioimmunotherapy efficacy combines radiobiological and immunological mechanisms, and only one study reported the benefits of FDG-PET in radioimmunotherapy efficacy assessment.[24] The aim of this prospective study was to evaluate the usefulness of FDG-PET imaging, performed using an integrated PET/CT system, to predict response to fractionated radioimmunotherapy with ^{90}Y-epratuzumab in refractory NHL patients included in an ongoing phase-I/II radioimmunotherapy trial. This is the first study assessing FDG-PET as a monitor of fractionated radioimmunotherapy.

Design and Methods

Patients

The study was approved by the respective ethics committees and all patients gave their informed consent before enrollment. Patients in this study were enrolled in Nantes or Lille (France) as part of a large, multi-center, phase I/II dose-escalation study of fractionated radioimmunotherapy with ^{90}Y-epratuzumab. Study subjects were males and females, over 18 years of age, with histologically-confirmed B-cell NHL (any histological grade by REAL classification) who failed after at least 1 regimen of standard chemotherapy and presented with measurable disease by CT, but no single mass with a dimension in any direction greater than 10 cm., and with less than 25% bone marrow involvement. At least four weeks had passed since any prior chemotherapy, any major surgery, or any radiation therapy. Patients had not received prior external radiation including more than 25% of the red marrow or exceeding the maximum tolerable levels for critical organs, and had adequate performance status (Karnofsky > 70%), serum chemistries (serum creatinine < 1.5 mg/dL or creatinine clearance > 50 mL/min; bilirubin < 2 mg/dL) and hematology (hemoglobin > 10 g/dL, WBC > 3,000/mm^3, granulocytes > 1,500/mm^3, platelets > 100,000/mm^3 without transfusions or cytokines for support).

Antibody preparation and administration

Immunomedics, Inc. (Morris Plains, NJ, USA) provided epratuzumab conjugated with the macrocyclic chelating agent 1,4,7,10-tetra-azacyclodecane-N,N',N",N"'-tetra-acetic acid (DOTA-epratuzumab), as well as unconjugated epratuzumab. Radiolabeling of DOTA-epratuzumab, purification of the radiolabeled antibody, and immunoreactivity tests were performed as previously described.[11] Patients received 1 or 2 courses of fractionated radioimmunotherapy. Each course consisted of 2 or 3 infusions of 92.5–370 MBq/m^2 (2.5–10 mCi/m^2) ^{90}Y-epratuzumab, resulting in a cumulative administered activity of 185–1,110 MBq/m^2 (5–30 mCi/m^2). The 2 or 3 infusions of ^{90}Y-epratuzumab were administered one week apart. Unlabeled epratuzumab was added to achieve a total antibody dose of 1.5 mg/kg/infusion.

Conventional diagnostic methods

Response to radioimmunotherapy was evaluated with conventional diagnostic methods consisting of clinical examination, CT, laboratory screening, and bone marrow biopsy if bone marrow was involved at baseline, and classified according to the International Workshop Response Criteria (IWC).[25] Evaluation was performed at baseline and at six weeks after each course of radioimmunotherapy. Additional imaging took place every three months until progression of disease. Baseline and follow-up helical CT scans of neck, chest, abdomen, and pelvis were obtained using intravenous contrast. Diagnostic contrast-

enhanced CT scans were performed in a variety of radiological institutes, since the two hospitals both serve as tertiary centers. CT scans were performed using the appropriate protocol and guidelines for lymphoma staging. Each CT scan was reported initially by the scanning radiologist and usually reviewed by a second radiologist specializing in lymphoma imaging in each of the two participating centers (Nantes and Lille). Based on resultant bidimensional tumor size measurements, response was categorized according to IWC criteria as CR (complete response, complete disappearance of all disease-related radiological abnormalities, with negative bone marrow biopsy, and no other assessable disease), CRu (unconfirmed CR, one or more residual tumors originally greater than 1.5 cm in diameter that regressed by at least 75% in the sum of the products of the two longest perpendicular diameters, SPD), PR (partial response, a reduction of at least 50% in SPD of the six largest measurable sites, and no new lesions), progressive disease (PD, a more than 25% increase from the nadir value in the SPD of measurable lesions or the appearance of a new lesion), or SD (stable disease, a less than 50% reduction or less than 25% increase from the nadir in the SPD of measurable lesions, with no new lesions). Time to progression (TTP) was measured from first infusion (beginning of radioimmunotherapy) until PD according to IWC criteria.

Response assessment by FDG-PET imaging

FDG-PET was performed at baseline and at six weeks after each course of radioimmunotherapy. Additional imaging took place every three months until progression of disease. Before each FDG-PET study, patients fasted for at least four hours and had capillary glucose levels measured with a glucometer. PET images were acquired 60-80 mins. after injecting 7 MBq/kg ^{18}F-FDG, using a DISCOVERY LS PET-CT imaging system (GE Medical Systems, Waukesha, WI, USA), and reconstructed by iterative algorithm (ordered-subset expectation maximization) with and without attenuation correction. FDG-PET images underwent blind evaluation by two nuclear medicine physicians, with foci of abnormal ^{18}F-FDG uptake considered positive and imaging findings reported regionally. For initial staging, positive FDG-PET was defined as the existence of areas of increased uptake thought to be lymphoma-related, and negative as the absence of all abnormal disease uptake. After radioimmunotherapy, metabolic response was defined according to international guidelines, PET-IHP,[21] as CR (PET negative, disappearance of all foci of abnormal ^{18}F-FDG uptake), PR (one or more PET-positive at previously involved site), SD (PET-positive at prior sites and no new sites), or PD (^{18}F-FDG uptake increased at a tumor site or the presence of new foci). TTP between first infusions of radioimmunotherapy until PD, as determined by international guidelines (PET-IHP), was measured.

Imaging performance analysis

For both ethical and practical reasons, not every suspected involved mass observed six weeks after radioimmunotherapy was evaluated by histology. The gold standard was therefore determined on the basis of histology and follow-up according to IWC criteria. The discriminatory accuracy of the diagnostic tests was calculated for each conventional diagnostic method and PET early response measurement (six weeks after radioimmunotherapy). A positive finding on conventional methods (SD or PD) or PET (PR or PD) was considered as true-positive if confirmed by histopathology or by follow-up with a short TTP (maximum six months), according to IWC criteria. A false-positive was a positive finding on a diagnostic method and negative findings on histopathology and follow-up (TTP greater than six months). A negative finding on a conventional method (CR, CRu, PR) or PET (CR) was considered to be true-negative if a TTP greater than six months was observed. A negative finding on a conventional method or PET was considered to be false-negative if a short TTP was observed. Evaluation of the prognostic value of PET results at six weeks post-radioimmunotherapy was based on TTP outcome (according to IWC criteria), with significance evaluated by log-rank statistics (STATA/SE Software, Version 10.0; StataCorp, College Station, Texas, USA). Only patients with at least six months of follow-up without progression were considered assessable. TTP of patients with early negative-PET and early positive-PET were compared. TTP of patients with objective response at six weeks according to IWC criteria (CR, CRu, PR) and no objective response at the same time point, according to IWC criteria (SD, PD), were compared.

Results

Patients' characteristics

Patients' characteristics at study entry are summarized in Table 1. Twenty-seven patients (14 males, 13 females; 46–83 years old, 14 from Nantes and 13 from Lille), with either FL (n=16), MALT (n=2), diffuse large B-cell lymphoma (DLBCL) (n=3), or mantle-cell lymphoma (n=6) were enrolled after failing prior treatments (chemotherapy, n=27; rituximab, n=23; external beam radiation therapy, n=4; stem cell support, n=5). At study entry, conventional diagnostic methods identified sites of disease in each patient involving 1–12 regions (median, 3). PET imaging confirmed disease in 94/99 regions identified by CT, and identified 42 additional regions of disease in 16 patients, with upstaging (Ann Arbor classification) in 4. During this study, 24 patients received 1 course of radioimmunotherapy, while the other 3 patients were each retreated once with three months (n=1) or six months (n=2) between courses.

Post-therapy conventional diagnostic methods results

Based on conventional restaging methods, 21 patients

achieved objective responses (4 CR's, 11 CRu's, 6 PR's) after one course of radioimmunotherapy (Table 2). Thirteen patients with objective responses had disease progression detected 3–25 months post-radioimmunotherapy, while the other patients remain in remission with no evidence of disease progression at the last assessment. Six patients did not achieve objective responses after 1 course of radioimmunotherapy, including 3 patients with PD at first post-radioimmunotherapy evaluation, and 3 patients had SD. One of the 3 patients with SD was retreated at three months and continued to maintain stable disease before disease progression was detected at the six-month evaluation. Two patients with CRu's were also retreated when their disease progressed six months after the first course of radioimmunotherapy. One patient again achieved a CRu response which lasted for six months before disease progression occurred, while the other patient initially had stable disease after the second course of radioimmunotherapy before disease progression occurred at three months.

Post-therapy FDG-PET results

Post-therapy (including post-retreatment in 3 patients), a total of 81 PET studies were evaluated as CR (n=34), PR (n=24) or PD (n=23), compared with CR (n=12), CRu (n=31), PR (n=15), SD (n=8) or PD (n=15) when tumor responses at the same time points were classified by IWC criteria. Of 50 responses not evaluated as CRu by IWC criteria, PET findings agreed with 42 (84%) responses determined by conventional IWC criteria (15 PD/PD, 10 CR/CR, 17 SD-PR/PR), but PET identified 4 PD when responses were evaluated as 2 CR and 2 PR, and identified 4 CR when responses were evaluated as PR. Of the 31 responses evaluated as CRu by conventional methods, 20 (65%) were found to be negative for disease (CR) by PET, but the other 11 (35%) were determined to be positive for disease (7 PRs and 4PDs).

Of the 29 early assessments obtained at six weeks post-therapy (26 after the first course, 3 after the second course), PET studies at that time point were negative in 11 (11 CR) and positive in 18 cases (15 PR and 3 PD), while tumor responses were classified as CRu (n=14), PR (n= 8), SD (n=5), and PD (n=2) by IWC criteria. No CR was observed using IWC criteria. Among the 15 responses not evaluated as CRu by CT, the early PET findings were positive in 13 (87%) cases (2 PD/PD, 11 SD-PR/PR) and negative in 2 (13%). Among the 14 responses evaluated as CRu by CT, 5 PET findings were positive (4 PR, 1 PD) and 9 were negative. A positive PET and negative PET study are shown in Figures 1 and 2 respectively. Twenty-two imaging studies were available for the six weeks post-radioimmunotherapy analysis and all were included.

Table 1. Patients' characteristics.

Pt s	*Age sex*	*NHL subtypes*	*Prior therapy*	*Regions with disease identified by CDM*		*Additional regions of disease identified by PET*	*Injected activity (MBq/m² x wks)*	
				Confirmed by PET	*Negative by PET*		*1st RIT*	*2nd RIT*
1	67F	FL	C, XRT, R	1	-	-	277 x 3	277 x 3
2	71M	FL	C, XRT, R	1	-	-	370 x 2	-
3	46F	FL	C, XRT, R	4	-	8	277 x 2	277 x 2
4	46F	FL	C, SCS, R	3	-	2	92.5 x 3	-
5	52F	FL	C, XRT, R	2	1	2	277 x 3	277 x 3
6	65F	DLBCL	C, R	2	-	3	370 x 3	-
7	48M	FL	C, SCS	5	-	3	185 x 2	-
8	61M	DLBCL	C, SCS	2	-	-	185 x 2	-
9	47M	FL	C	3	1	3	370 x 3	-
10	68M	FL	C, R	6	1	6	92.5 x 2	-
11	60M	FL	C,R	2	-	-	92.5 x 3	-
12	46M	MCL	C,R	1	-	1	370 x 3	-
13	53F	MALT	C, SCS, R	1	-	1	92.5 x 3	-
14	67M	FL	C, SCS	1	-	1	92.5 x 3	-
15	56F	MALT	C, R	4	-	1	466 x 2	-
16	77F	DLBCL	C, R	7	-	4	466 x 2	-
17	83F	MCL	C, R	4	-	-	466 x 2	-
18	72M	FL	C, R	2	1	-	466 x 2	-
19	67F	MCL	C, R	12	-	-	466 x 3	-
20	68M	MCL	C, R	4	-	-	466 x 3	-
21	74M	MCL	C, R	3	-	2	555 x 2	-
22	67M	MCL	C, R	4	-	-	555 x 2	-
23	72M	FL	C, R	3	-	-	555 x 2	-
24	68F	FL	C, R	3	-	-	555 x 2	-
25	60F	FL	C, R	4	-	1	555 x 2	-
26	63M	FL	C,R	1		2	555 x 2	
27	68F	FL	C,R	9	1	2	555 x 2	

FL: follicular lymphoma, DLBCL: diffuse large B-cell lymphoma, MCL: mantle cell lymphoma, C: chemotherapy, XRT: external radiotherapy, R: rituximab, SCS: stem cell support, CDM: conventional diagnostic imaging including clinical examination, CT and bone marrow biopsy.

Among these PET images, the mean TTP according to IWC criteria was 15.6±3.6 months [95% CI=8.6-22.7] (14.0±11.0 months according to metabolic PET-IHP guidelines) when PET was negative for disease (CR), compared with 5.4±0.8 months [95% CI = 3.7-7.1] (4.6±3.4 months according to metabolic PET-IHP guidelines) when PET was positive for disease (PR or PD) (p=0.008). In comparisons, early evaluation performed using conventional methods showed a lower difference between SD and PD non-responders (4.0±1.1 months) [95% CI=1.8-6.2] and CR, CRu and PR responders (10.4±2.1 months) [95% CI=6.4-14.4] (p=0.016). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET six weeks after radioimmunotherapy were 86%, 62%, 80%, 71% and 77% respectively (kappa=0.49, p<0.01), compared with 36%, 87%, 83%, 44% and 55% respectively (kappa=0.19, p<0.12) using conventional methods. In addition, among the 12 patients showing a metabolic CR, this was observed as early as six weeks in 11 cases (92%) and after six weeks in only 1 patient (8%).

Discussion

The limitations of conventional CT-based disease assessment in NHL are well-known. These are due to its dependence on anatomical criteria, since lymph nodes less than 1 cm may harbor malignancy while larger nodes are not necessarily malignant. This problem is compounded when evaluating treatment response, since

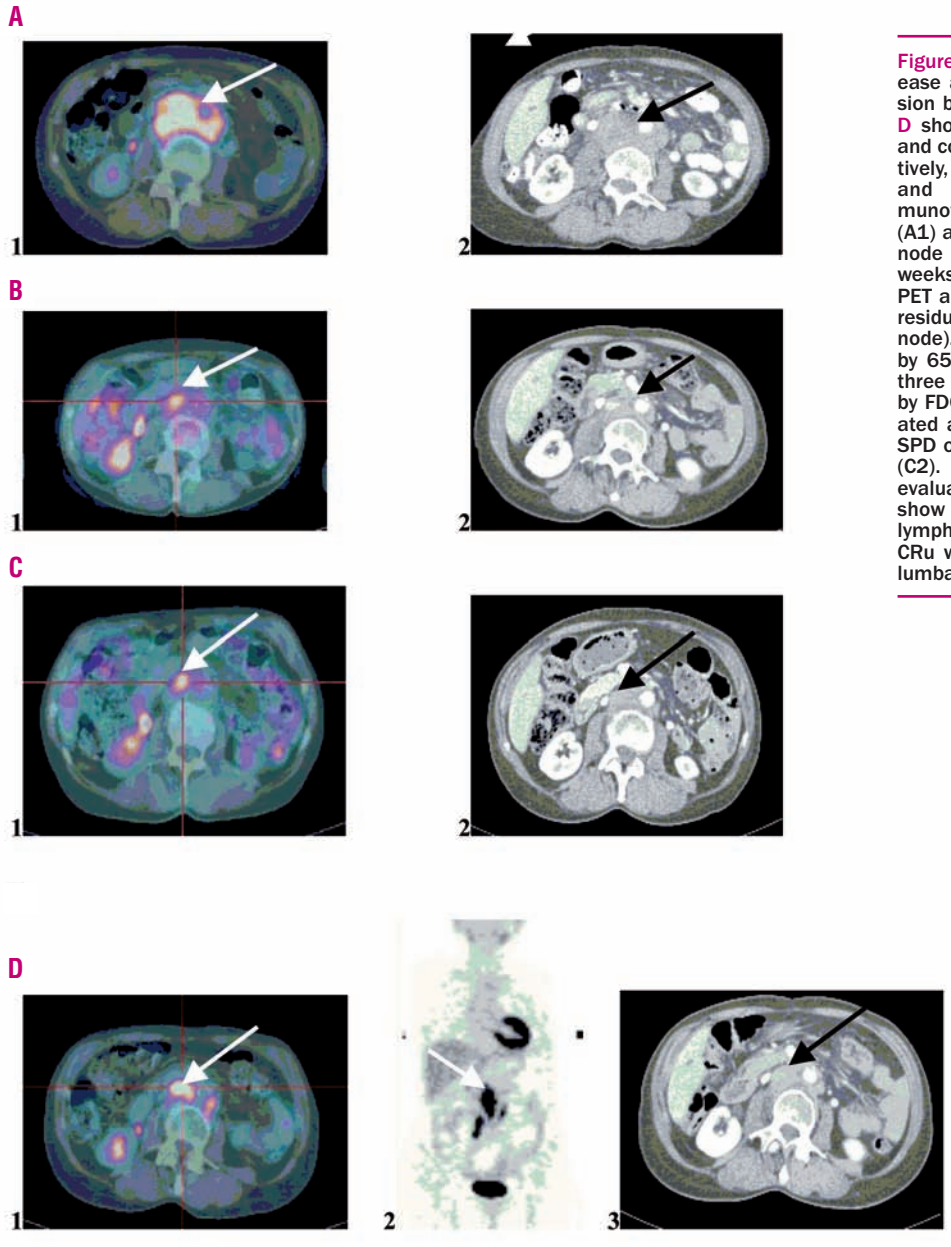

Figure 1. Detection of residual disease and early detection of progression by FDG-PET. Images A, B, C and D show FDG-PET and CT transverse and coronal images recorded, respectively, before RIT and six weeks, three and six months after radioimmunotherapy. Pre-treatment FDG-PET (A1) and CT (A2) show lumbar lymph node involvement. Response at six weeks was evaluated as PR by FDG-PET and CT (B1 and B2 arrows show residual masses in lumbar lymph node). The lesion has been reduced by 65% on CT images. Response at three months was evaluated as PR by FDG-PET (C1), while CT was evaluated as CRu with a reduction of the SPD of 80% compared with baseline (C2). FDG-PET at six months was evaluated as PD (D1 and D2: arrows show increase of size of lumbar lymph nodes), while CT confirmed CRu with a reduction of 84% of the lumbar mass (D3).

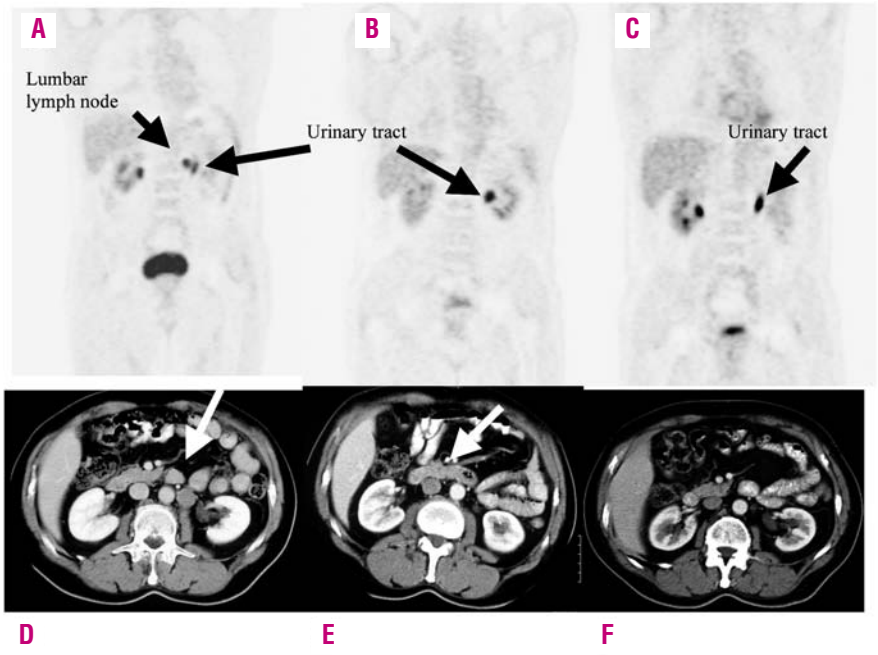

Figure 2. Early detection of complete response by FDG-PET. A, B, and C show FDG-PET coronal images recorded, respectively, before radioimmunotherapy and six weeks and three months after radioimmunotherapy. D, E, and F show CT transverse images performed, respectively, before radioimmunotherapy and six weeks and 18 months after radioimmunotherapy. Pre-treatment imaging shows one lumbar lymph node (A: black arrows show lumbar abnormal focus and normal urinary tract, D: white arrow shows lumbar lymph node). Response at six weeks was evaluated as CRu by CT (E: white arrow shows lumbar lymph node with 80% decrease) and CR by FDG-PET (B: black arrow shows normal urinary tract). CT three months later confirmed the CR, and successive serial CT and PET imaging documented continuing CR, including the negative image obtained at 18 months (F).

Table 2. Post-radioimmunotherapy imaging results.

Pts	*Best response according to PET*	*Best response according to CDM*	*TTP according to CDM*	*Post-radioimmunotherapy serial imaging results*									
				6 weeks		*3 months*		*6 months*		*9 months*		*12 months*	
				CT	*PET*	*CT*	*PET*	*CT*	*PET*	*CT*	*PET*	*CT*	*PET*
1	CR	CRu	6 mo	CRu	CR	CRu	CR	PD	PD	-	-	-	-
1*	CR	CRu	6 mo	CRu	CR	CRu	PD	PD	PD	-	-	-	-
2	CR	CR	24+ mo	CRu	CR	CR	CR	CR	CR	CR	CR	CR+**	CR+**
3	PR	CRu	6 mo	CRu	PR	CRu	PR	PD	PD	-	-	-	-
3*	PR	SD	3 mo	SD	PR	PD	PD	-	-	-	-	-	-
4	PD	CRu	3 mo	CRu	PD	PD	PD	-	-	-	-	-	-
5	PR	SD	3+ mo	SD	PR	SD	PR	-	-	-	-	-	-
5*	PR	SD	6 mo	SD	PR	SD	PR	PD	PD		-	-	-
6	CR	CR	9mo	CRu	CR	CR	CR	CR	PD	PD	-	-	-
7	CR	CRu	9mo	CRu	CR	CRu	CR	CR	PD	PD	PD	-	-
8	PD	PD	3 mo	-	-	PD	PD	-	-	-	-	-	-
9	PR	CRu	6 mo	CRu	PR	CRu	PD	PD	PD	-	-	-	-
10	PD	PD	6 wk	PD	PD	-	-	-	-	-	-	-	-
11	PR	SD	3 mo	SD	PR	PD	-	-	-	-	-	-	-
12	PR	PR	6 mo	PR	PR	PR	PR	PD	-	-	-	-	-
13	CR	CRu	28+ mo	CRu	CR	CRu	CR	CRu	CR	CRu	CR	CRu	CR
14	PR	CRu	12 mo	CRu	PR	CRu	PR	-	-	CRu	PD	PD	
15	CR	CR	25 mo	CRu	CR	CRu	CR	CR	CR	CR	CR	CR	CR
16	PD	PD	6 wk	PD	PD	-	-	-	-	-	-	-	-
17	PR	CRu	3 mo	CRu	PR	PD	PD	-	-	-	-	-	-
18	PR	SD	9 mo	SD	PR	SD	PR	NP	NP	CP	-	-	-
19	PR	PR	12 mo	PR	PR	PR	PR	PR	PR	-	-	PD	PD
20	PR	PR	4 mo	PR	PR	PD	PD	-	-	-	-	-	-
21	CR	CRu	6+ mo	CRu	CR	CRu	CR	CRu	CR	-	-	-	-
22	CR	PR	6+ mo	PR	CR	PR	CR	PR	PD	-	-	-	-
23	PR	PR	6 mo	PR	PR	PR	PD	PD	PD	-	-	-	-
24	CR	PR	3+ mo	PR	CR	PR	CR	-	-	-	-	-	-
25	PR	PR	6+ mo	PR	PR	CRu	PR	CRu	PD	-	-	-	-
26	CR	CRu	3+mo	PR	PR	CRu	CR	-	-	-	-	-	-
27	CR	CRu	6+wk	CRu	CR	-	-	-	-	-	-	-	-

**Retreatment. **CR response by both CT and PET continuing at 18 months and last evaluation at 24 months. CDM: conventional diagnostic imaging, CR: complete response, CRu: CR unconfirmed, PD: progression of disease, IR: incomplete response, SD: stable disease, PR: partial response.*

morphological reductions occur slowly and incompletely over time, and post-treatment fibrosis remains difficult to differentiate from residual disease.[21] By reflecting glucose metabolism, FDG-PET provides an independent means of assessing malignancy, and several studies showed that FDG-PET imaging was more accurate than conventional imaging methods for assessment of lymphoma response to chemotherapy and chemo-immunotherapy.[21-22] FDG-PET is useful in this setting because it can distinguish between viable tumor and necrosis or fibrosis in residual masses often present in patients without any other clinical or biochemical evidence of active disease. In contrast to chemotherapy, glucose metabolism may decrease more slowly after radioimmunotherapy, because of inflammatory radiation damage. For external radiation therapy, Greven *et al.*[26] observed that FDG-PET studies in head and neck cancer one month after treatment predicted outcome less accurately than studies performed at four months, while Castellucci[27] found that out of 16 FDG-PET studies performed approximately 40 days after radiation therapy, only 3 showed a slight increase. The only previous study of tumor response assessment following radioimmunotherapy that we are aware of found that FDG-PET imaging one to two months after radioimmunotherapy correlated with response by conventional assessment, while imaging five to seven days after radioimmunotherapy did not.[24]

In this study, FDG-PET imaging was evaluated following 1 or 2 courses of fractionated radioimmunotherapy with ^{90}Y-epratuzumab. The patients in the study were only a small proportion of a larger population of NHL patients included in an on-going phase I/II clinical trial. Because the new imaging method assessed was FDG-PET, and even if FDG-PET appeared more accurate than conventional diagnostic methods, the TTP used for statistical comparison was determined using conventional methods (defined as the gold standard). Consistent with the other imaging studies, FDG-PET in this setting appeared more accurate than conventional CT in evaluating response. In particular, FDG-PET imaging six weeks after treatment appeared to be reliable for early disease assessment, and for CT scans frequently evaluated as CRu, FDG-PET was able to remove any doubts concerning residual disease. Positive FDG-PET findings six weeks after radioimmunotherapy predicted significantly earlier relapse compared with negative results. Surprisingly, the best metabolic response could be defined as soon as six weeks after treatment in more than 90% of cases. These observations support the view that radiation-induced inflammation is probably not so important after radioimmunotherapy (low-dose-rate irradiation) compared with external radiotherapy (high-dose-rate irradiation) which induces more necrosis and less apoptosis than internal-targeted radiotherapy. Radioimmunotherapy cytotoxicity combines radiobiological and immunological effects. The radiobiological effects are predominant and are reflected by a metabolic response during the six weeks following radiolabeled antibody injection. The immunological effects, probably underestimated in this population of previously heavily-treated patients, are probably implicated in the decrease of FDG uptake after the six week evaluation, but this must still be confirmed.

Since FDG-PET combined with CT are the reference methods according to the IHP consensus for response assessment at the conclusion of front-line, salvage or high-dose therapy using chemotherapy, chemo-immunotherapy or external radiotherapy, it is interesting to confirm these imaging methods for assessment of radioimmunotherapy, the use of which is increasing, in particular in front-line or salvage, non-myeloablative or myeloablative treatment. The use of radioimmunotherapy has mainly been confirmed for FL, but its benefits in other subtypes of lymphoma have also been suggested in recent studies.[28,29] The role of metabolic information after treatment for Hodgkin's lymphoma and diffuse large B-cell lymphoma is clear, given that these are curable diseases.[21,23] The role of FDG-PET for treatment evaluation of indolent lymphoma, such as follicular lymphoma or mantle-cell lymphoma, is less evident. For these most often incurable types of NHL, progression-free or overall survival is generally the primary end-point in clinical trials. However, if overall objective response rate and, in particular, complete response rate are major end-points, FDG-PET may be used for their more accurate determination, according to IHP consensus.[21]

Conclusions

Our results in this small group of patients indicate that radioimmunotherapy responders may be identified with FDG-PET more accurately than with CT, and demonstrate the benefit of using FDG-PET to detect residual disease as soon as six weeks post-radioimmunotherapy.

Authorship and Disclosures

Conception and design: FK-B, CB-M, DH. Provision of study materials or patients: J-LH, SLG, TG, FM, DMG, WAW. Collection and assembly of data: FK-B, CB-M, DH. Data analysis and interpretation: FK-B, CB-M, DH, BD. Manuscript writing: FK-B, CB-M, DH. Final approval of manuscript: FK-B, CB-M, DH, DMG, WAW. Statistical analysis: LC. The authors reported no potential conflicts of interest.

References

1. Goldenberg DM, Sharkey RM. Advances in cancer therapy with radiolabeled monoclonal antibodies. Q J Nucl Med Mol Imaging 2006;50: 248-64.
2. Chatal JF. Radioimmunotherapy, a new breakthrough in the treatment of follicular non-Hodgkin's lymphoma: the European perspective. Cancer Biother Radiopharm 2006; 21:1-4.
3. Kaminski MS, Zasadny KR, Francis IR, Milik AW, Ross CW, Moon SD, et al. Radioimmunotherapy of B-cell lymphoma with [131I]anti-B1 (anti-CD20) antibody. N Engl J Med 1993; 329:459-65
4. Wagner HN Jr, Wiseman GA, Marcus CS, Nabi HA, Nagle CE, Fink-Bennett DM, et al. Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with (90)Y-labeled anti-CD20 monoclonal antibody. J Nucl Med 2002;43:267-72.
5. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20: 2453-63.
6. Wiseman GA, Kornmehl E, Leigh B, Lamonica D, Kornmehl E, Spies SM, et al. Radiation dosimetry results and safety correlations from 90Y-ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin's lymphoma: combined data from 4 clinical trials. J Nucl Med 2003;44:465-74.
7. Goldenberg DM, Horowitz JA, Sharkey RM, Hall TC, Murthy S, Goldenberg H, et al. Targeting, dosimetry, and radioimmunotherapy of B cell lymphomas with iodine-131-labeled LL2 monoclonal antibody. J Clin Oncol 1991;9:548-64.
8 Juweid M, Sharkey RM, Markowitz A, Swayne LC, Rubin AD, Hanley D, et al. Treatment of non-Hodgkin's lymphoma with radiolabeled murine, chimeric, or humanized LL2, an anti-CD22 monoclonal antibody. Cancer Res 1995;55: 5899s-907s.
9. Juweid M, Stadtmauer E, Sharkey RM, Sharkey RM, Suleiman S, Luger S, et al. Pharmacokinetics, dosimetry and initial therapeutic results with 131I- and 111In-/90Y-labeled humanized LL2 anti-CD22 monoclonal antibody in patients with relapsed/refractory non-Hodgkin's lymphoma (NHL). Clin Cancer Res 1999;5:3292s-303s.
10. Sharkey RM, Brenner A, Burton J, Hajjar G, Toder SP, Alavi A, et al. Radioimmunotherapy of non-Hodgkin's lymphoma with 90Y-DOTA humanized anti-CD22 IgG (90Y-epratuzumab): do tumor targeting and dosimetry predict therapeutic response? J Nucl Med 2003; 44:2000-18.
11. Lindén O, Hindorf C, Cavalin-Stahl E, Wegener WA, Goldenberg DM, Horne H, et al. Dose-fractionated radioimmunotherapy in non-Hodgkin's lymphoma using DOTA-conjugated, 90Y-radiolabeled, humanized anti-CD22 monoclonal antibody, epratuzumab. Clin Cancer Res 2005;11:5215-22.
12. Griffiths GL, Govindan SV, Sharkey RM, Fisher DR, Goldenberg DM. 90Y-DOTA-epratuzumab: an agent for radioimmunotherapy of non-Hodgkin's lymphoma. J Nucl Med 2003;44:77-84.
13. Juweid ME, Cheson BD. Role of positron emission tomography in lymphoma. J Clin Oncol 2005;23: 4577-80.
14. Juweid ME. Utility of positron emission tomography (PET) scanning in managing patients with Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2006;259-65, 510-1.
15. Juweid ME, Wiseman GA, Vose JM, Ritchie JM, Menda Y, Wooldridge JE, et al. Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. J Clin Oncol 2005;23:4652-61.
16. Spaepen K, Stroobants S, Dupont P, Van Steenweghen S, Thomas J, Vandenberghe P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F] FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnosis methods? J Clin Oncol 2001;19:414-19.
17. Kostakoglu L, Coleman M, Leonard JP, Kuji I, Zoe H, Goldsmith SJ, et al. PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease. J Nucl Med 2002;43:1018-26.
18. Haioun C, Itti E, Rahmouni A, Brice P, Rain JD, Belhadj K, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 2005;106: 1376-81.
19. Mikhaeel NG, Hutchings M, Fields PA, O'Doherty MJ, Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol 2005;16:1514-23.
20. Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 1999;94:429-33.
21. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007; 25:571-8.
22. Kelloff GJ, Sullivan DM, Wilson W, Cheson B, Juweid M, Mills GQ, et al. FDG-PET Lymphoma Demonstration Project Invitational Workshop. Acad Radiol 2007;14: 330-9.
23. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. The International Harmonization Project on Lymphoma Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.
24. Torizuka T, Zasadny K, Kison P, Rommelfanger SG, Kaminski MS, Wahl RL. Metabolic response of non–Hodgkin's lymphoma to 131I-anti-B1 radioimmunotherapy: evaluation with FDG-PET. J Nucl Med 2000;41:999-1005.
25. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999;17:1244-53.
26. Greven KM, Williams DW, Keys JW Jr, McGuirt WF, Watson NE Jr, Randall ME, et al. Positron emission tomography of patients with head and neck carcinoma before and after high dose radiation. Cancer 1994; 74:1355-59.
27. Castellucci P, Zinzani P, Nanni C, Farsad M, Moretti A, Alinari L, et al. 18F-FDG PET early after radiotherapy in lymphoma patients. Cancer Biother Radiopharm 2004;19:606-12.
28. Morschhauser F, Illidge T, Huglo D, Martinelli G, Paganelli G, Zinzani PL, et al. Efficacy and safety of yttrium-90 ibritumomab tiuxetan in patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for autologous stem-cell transplantation. Blood 2007;110:54-8.
29. Gopal AK, Rajendran JG, Petersdorf SH, Maloney DG, Eary JF, Wood BL, et al. High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. Blood 2002;99:3158-62.