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The online version of this article contains a supplemental appendix.

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A possible role of ^{18}F-FDG positron-emission tomography scanning in the early detection of rituximab-induced pneumonitis in patients with non-Hodgkin's lymphoma

Rituximab is safe and effective in the treatment of patients with non-Hodgkin's lymphoma (NHL). Rituximab is generally well-tolerated. Its major adverse effects are infusion related and include fever, chills, dyspnea and hypotension. Dyspnea is a frequent complaint in NHL patients, and is often related to anemia or general fatique. However, it may also be the first sign of a severe underlying disease. Recently, rituximab-induced pneumonitis (RP) has been reported as side-effect of rituximab, often presenting with complaints of dyspnea.[1-11] [^{18}F]-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) is currently a routine modality in the early diagnosis and follow-up of NHL patients. ^{18}F-FDG PET may show abnormalities other than lymphoma activity.

We describe 4 patients with dyspnea related to RP, in which ^{18}F-FDG PET proved to be of diagnostic value. We performed a single center, retrospective case-control study of NHL patients treated with C[H]OP-rituximab for the period January 1, 2003 - April 30, 2007 (51 months) to investigate variables associated with RP and to investigate the abnormalities found on ^{18}F-FDG PET. For this case-control study, we included patients with a documented ^{18}F-FDG PET before rituximab therapy and in whom *a priori* the lymphoma response was evaluated by ^{18}F-FDG PET within six weeks after finishing the C[H]OP-rituximab therapy. Patients who received simultaneously, or in the past, chemotherapy-regimens other than C[H]OP were excluded.

RP was defined as the presence of characteristic clinical findings such as dyspnea, fever, cough, and the presence of diffuse unilateral or bilateral pulmonary activity detected by ^{18}F-FDG PET during the treatment with rituximab. Consolidations or ground-glass opacities on chest x-ray or high-resolution computed tomography (HRCT) were considered as supportive findings for the diagnosis of RP. The diagnosis RP was only made after exclusion of other causes of diffuse lung disease.

All subjects were reviewed for clinical, laboratory, and radiological characteristics. Treatment schedules were reviewed for the body surface-adjusted and cumulative dose of rituximab and for the dose-interval. In patients with an RP, an extensive search for other diseases was performed. This included analysis of blood, sputum and bronchoalveolar lavages (BAL). BAL was cultured for a broad panel of respiratory pathogens, i.e. common bacteria, *Legionella*, *Chlamydia*, *Pneumocystis*, mycobacteria, fungi and viruses such as *Adenovirus*, *Para-*, and Influenza virus. Polymerase chain reaction was performed for common viruses, *Chlamydia*, *Legionella* and mycoplasma. In addition, immunophenotyping of white blood cells in the BAL was performed. Pulmonary function and carbon monoxide diffusion tests were carried out. Chest X-ray and HRCT were reviewed for other abnormalities. ^{18}F-FDG PET were analyzed for activity pattern and maximum Standardized Uptake Values (SUV_{max}). SUV_{max} was corrected for body weight. Serial ^{18}F-FDG PET were performed to detect the time to disappearance of the increased FDG-uptake. Patients with RP were considered as cases (case group) and were compared with patients without RP (control group).

Statistical analysis was performed with SPSS 15.0 software (SPSS Inc, Chicago, Illinois, USA). The number of

administered doses of rituximab is expressed as median, while the total amount of rituximab is given as mean. Continuous variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed by Pearson's χ^2 test. The effect of each variable adjusted for the others was assessed by logistic regression analysis. A p value <0.05 was considered to be statistically significant.

In the period from January 2003 till April 2007, a total of 36 patients were treated with R-C[H]OP, including 4 patients (cases) in which RP was diagnosed (Table 1). The remaining 32 out of 36 patients formed the control group. The control group consisted of 21 (65.5%) males and had a mean age of 60.7 years (range: 17-88 years). The control group was most frequently diagnosed with diffuse large B-cell lymphoma (21; 65.5%) or follicular lymphoma (7; 21.9%).

The cases and controls were comparable for age, gender, NHL-classification, Ann Arbor stage and treatment schedule. There were no differences between the cases and the controls with regard to laboratory parameters, number of administered rituximab doses and interval of rituximab administration. The cumulative dose of administered rituximab was also not different between the case group (4125mg; range: 2000-5600) and the control group (4820mg; range: 700-9860).

All 4 patients with RP showed bilateral diffuse pulmonary uptake on ^{18}F-FDG PET (*Online Supplementary Figure S1*). The mean SUV_{max} was 3.5 (range 1.5-7.8). In one patient ^{18}F-FDG PET abnormalities preceded abnormalities found on HRCT and chest X-ray. The activity on ^{18}F-FDG PET was reversible in 3 of the 4 patients after discontinuation of rituximab and after administration of corticosteroids. Pulmonary activity was reversible after discontinuation of rituximab in one patient, who did not receive steroids. Pulmonary activity on ^{18}F-FDG PET was seen up to five months after the last rituximab administration, and up to four months after abnormalities were noted on ^{18}F-FDG PET. No abnormalities were noted on ^{18}F-FDG PET in the control group.

A total of 20 cases of RP have been reported in the literature. According to the drug's manufacturer, the calculated reporting rate of all cases of possible rituximab-induced lung injury is currently less than 0.03%. The calculated incidence of RP based on reported cases to the manufacturer is less than 0.01%.[12] The calculated 4-year incidence of RP in our study was, however, 11%. The single center setting of our study might induce an observer bias. Larger, prospective studies are warranted to investigate the true incidence of RP.

The exact etiology of RP is not known. It is observed with a delay of onset between days to months. Burton *et al.* postulate that the release of cytokines, as tumor necrosis factor-α, interferon γ, interleukin-6, interleukin-8, are responsible for the induction of RP.[1] Other possible mechanisms of induction are complement activation or indirect cytotoxic T-lymphocyte activation.[4] Cytotoxic T-lymphocyte activation appears to be induced by dendritic cells that mature under the influence of cell-derived peptides resulting from rituximab-induced tumoral destruction. The activated cytotoxic T-lymphocyte may produce vascular and alveolar damage and thereby initiate lung injury. Cytotoxic T-lymphocyte activation may also be the result of interaction between rituximab and CD-20 positive T-cells, or by cross-reactivity between lung and tumoral antigens.

In the reported cases of RP, only Herishanu *et al*. mention the presence of subpleural unilateral activity on a midtreatment PET/CT.[4] The 4 patients in our study, all showed diffuse bilateral pulmonary uptake on ^{18}F-FDG PET imaging. HRCT and chest X-ray performed at the same time as the ^{18}F-FDG PET was normal in one person. This is probably due to the early detection of metabolic changes by ^{18}F-FDG PET. Although the uptake pattern in RP is not specific, it can be easily separated from recurrence of NHL.

In conclusion, the use of ^{18}F-FDG PET for lymphoma response may show other abnormalities as a result of chemotherapy or rituximab administration. We described 4 patients with dyspnea, in whom ^{18}F-FDG PET imaging proved to be a useful and early diagnostic tool in the detection of RP. Larger, prospective studies are warranted to investigate the significance of pulmonary abnormalities detected by ^{18}F-FDG PET in NHL patients receiving rituximab. RP results in clinical findings in combination with

Table 1. Features of non-Hodgkin's lymphoma patients with rituximab induced pneumonitis.

Case	Diagnosis	Treatment	Relation with treatment	Symptoms	HRCT	^{18}F-FDG PET	BAL	Treatment	Course
1. Male, 69 years	Diffuse large B-cell lymphoma, stage IIB	CHOP, rituximab 375 mg/m^2 (cycle 1 and 2), rituximab 187mg/m^2 (cycle 3-6), every 3 weeks	11 days after sixth cycle	Dyspnea	–	Diffuse, bilateral, SUV_{max} 7.8	–	none	Reversible
2. Female, 75 years	Diffuse large B-cell lymphoma, stage IVB	CHOP, rituximab 375 mg/m^2, every 2 weeks	3 days after fourth cycle	Dyspnea, Fever, cough, sputum	Consolidations, tree-in-bud sign, air trapping	Diffuse, bilateral, SUV_{max} 2.5	Lymphocyte 34,6%; CD4/CD8 ratio 1.2	Prednisone 30 mg daily	Reversible
3. Female, 54 years	Diffuse large B-cell lymphoma, stage IIIA	ICHOP, rituximab 375mg/m^2, every 2 weeks	8 days after seventh cycle	Cough, sputum, fever, dyspnea	Bilateral ground-glass opacities	Diffuse, bilateral, SUV_{max} 1.5	Lymphocyte 81.3% ; CD4/CD8 ratio 0.4	Prednisone 60 mg daily	Reversible
4. Female, 59 years	Diffuse large B-cell lymphoma, stage IVB	ICHOP, rituximab 375mg/m^2, every 2 weeks	After each two-weekly cycle	Dyspnea	Normal	Diffuse, bilateral, SUV_{max} 2.2	–	Prednisone 30 mg daily	Reversible

**CHOP: cyclophosphamide-doxorubicin-vincristine-prednisone; ICHOP: intensified cyclophosphamide-doxorubicin-vincristine-prednisone; HRCT: high-resolution computed tomography; ^{18}F-FDG PET, [^{18}F]-Fluorodeoxyglucose positron-emission tomography; BAL: bronchoalveolar lavages; SUV_{max}: maximum standardized uptake values.*

abnormalities on ^{18}F-FDG PET, sometimes in the absence of abnormalities on conventional radiological modalities. Rituximab is an important drug in the treatment of NHL patients; its withdrawal should, therefore, only be considered in symptomatic patients. RP proved to be reversible after discontinuation of rituximab in combination with administration of steroids or supportive care. More research has to be performed to confirm and quantify the association of rituximab and adverse lung reactions, to understand the underlying mechanism and to search for variables, predisposing for the development of RP.

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FDG-positron-emission tomography for staging and therapeutic assessment in patients with plasmacytoma

Plasmacytoma can be confined to bone (solitary bone plasmacytoma) or occur in extramedullary sites (extramedullary plasmacytoma).[1-4] Diagnostic criteria are a biopsy-proven lesion of bone or soft tissue with evidence of clonal plasma cells, normal bone marrow with no evidence of clonal plasma cells and absence of end-organ damage.[5,6] In a recent study, Zamagni *et al*. have shown that although MRI of the spine and pelvis still remains the gold standard imaging technique for the detection of bone marrow involvement in multiple myeloma, FDG-PET/CT provides additional and valuable information for the assessment of myeloma bone disease in areas not covered by MRI.[7] The purpose of the present study is a prospective comparison of FDG-PET/CT and MRI for the appraisal of the staging and the therapeutic assessment of patients with plasmacytoma.

Twenty-four patients (17 males and 7 females; median age 60 years, age range 35-78) with pathologically documented plasmacytoma were included from June 2003 to June 2007 at the University Hospital of Nantes (France). Patients underwent whole body FDG-PET/CT (also covering skull, upper and lower limbs) and bone marrow MRI at the initial staging and therapy afterwards. The physicians for the therapeutic assessment knew the primary site of the disease. For both ethical and practical reasons, not every suspected involved lesion was evaluated by histology. When histological data were not available, the gold standard, therefore, resulted from an exhaustive analysis of patient data and follow-up.

Twenty-three patients were assessed for pre-therapeutic staging and 14 for therapeutic staging. At baseline staging, 54 tumor sites were confirmed according to the gold standard: 50 in bone areas and 4 in soft tissue areas (head and neck, breast and pelvis).

For the baseline staging, overall 460 regions in 23 patients were analyzed by FDG-PET/CT and 120 regions in 20 patients compared to MRI. FDG-PET/CT showed abnormal uptake in 57 sites (53 in bone areas and 4 in soft tissue areas): 53 foci considered as true-positive (TP) and 4 foci as false-positive (FP). FDG-PET/CT missed 1 lesion (iliac bone) confirmed by biopsy. In the 120 regions explored by MRI, 29 lesions were confirmed as being plasmacytoma, according to the gold standard. MRI detected 32 abnormal images, 27 images considered as TP and 5 as FP. MRI missed 2 lesions. FDG-PET/CT correctly classified the 5 FP and the FN. In those areas, FDG-PET/CT showed 3 foci considered as FP and missed 1 lesion, all correctly classified by MRI. Se, Sp, PPV and PNV were calculated. Results are shown in Table 1.

The accuracies of MRI and FDG-PET/CT in detecting lesions were concordant in 12/20 patients (60%) and discordant for the remaining 8/20 (40%). Finally, in 10/20 patients (50%), FDG-PET/CT detected plasmacytoma lesions in 18 areas (bone: 8 patients, soft tissue: 2 patients), which were outside the scope. Figure 1 shows a lombar spine plasmacytoma detected by FDG-PET/CT and MRI.

For therapeutic evaluation, 14 FDG-PET/CT, corresponding to an overall 260 regions, were analyzed; 10 FDG-PET/CT (61 regions) compared with MRI. Five patients have been treated by radiotherapy, 6 by chemotherapy and 3 by high-dose chemotherapy and autologous stem cell transplantation. A complete response was observed in the 5 radiated patients and in 2 patients treated by chemother-