Doxorubicin Effect on Myocardial Metabolism as a Prerequisite for Subsequent Development of Cardiac Toxicity: Are There Unsuspected Confounders?

TO THE EDITOR: We have enthusiastically read the meticulous and well-conducted retrospective study by Bauckneht et al. published in the October issue of *The Journal of Nuclear Medicine* (*1*). The authors assessed the role of ^{18}F-FDG PET/CT in the prediction of doxorubicin cardiac toxicity in 69 patients treated with a chemotherapy regimen for Hodgkin lymphoma (HL); furthermore, they investigated the possible dose-dependent nature of doxorubicin toxicity in 15 athymic mice and concluded that in patients undergoing doxorubicin administration, not only is myocardial ^{18}F-FDG uptake increased but also that low ^{18}F-FDG uptake before chemotherapy may predict the development of cardiac toxicity.

Myocardial cells protect themselves from hypoxic state, reducing contractile function with the downregulation of hypoxia and mitochondrial oxidative metabolism through the "glucose-fatty acid cycle" (*2*), and ^{18}F-FDG uptake may be a useful tool to identify a myocardial metabolic switch subsequent to cellular damage (*3*).

Several published retrospective and preclinical studies, some already cited by Bauckneht et al. (*4,5*), suggest the opportunity of investigating the correlation between changes in myocardial ^{18}F-FDG uptake in pre- and postchemotherapy or radiotherapy evaluation and subsequent development of cardiac toxicity (*6,7*).

We also observed in a preliminary study that cardiac uptake of ^{18}F-FDG could increase during chemotherapy (*8*). Our first hypothesis was that in patients undergoing chemotherapy some elements may modify the variable avidity for glucose (*9*) and shift the myocardial metabolism from β-oxidation of fatty acids to glycolysis, also considering the possible role of steroids (for iatrogenic hyperglycemia) and granulocyte colony-stimulating factor (for insulinlike effects). We tested our hypothesis retrospectively in a group of HL patients ($n = 24$) treated with a regimen of adriamycin, bleomycin, vincristine, dacarbazine (ABVD) plus 20 mg of dexamethasone, excluding patients with antecedent cardiovascular disease, diabetes, and previous chemotherapy or mediastinal irradiation and identifying 10 patients who received from 50 to 575 mg of steroids additional to the standard (extra-steroids group).

All patients underwent ^{18}F-FDG PET/CT at staging, interim, and final evaluation: no significant differences were found between different scans in patients' body weight and glycemia levels at ^{18}F-FDG injection. We observed also an incremental trend in cardiac SUV_{max} at staging, interim, and final evaluation, and we found a significant association between ^{18}F-FDG uptake and extra-steroid administration ($P = 0.005$), suggesting a strong, independent (and possibly transient) correlation between administration of extra steroids and this phenomenon.

The correlation between cardiac toxicity after chemotherapy, in particular after anthracycline administration, or radiotherapy and myocardial ^{18}F-FDG uptake is a current study argument.

Given the aforementioned data, it is our opinion that ^{18}F-FDG PET/CT may be a useful biomarker of cardiac toxicity, but only after first clarifying the role of other factors that may occur as confounders in ^{18}F-FDG uptake, such as steroid administration.

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REPLY: We are grateful to Finessi et al. for their letter, which raises a crucial topic. We agree that many possible confounding factors may challenge the interplay between anthracycline-induced cardiotoxicity and myocardial ^{18}F-FDG accumulation. Among them, steroids might profoundly interfere with myocardial metabolism, increasing insulin resistance, reducing free fatty acid serum levels, and consequently potentially affecting myocardial ^{18}F-FDG uptake (*1*).

On the other hand, the relevance of corticosteroids nicely fits with our hypothesis about the existence of a peculiar ^{18}F-FDG metabolic pathway located in the endoplasmic reticulum and regulated by hexose-6-phosphate dehydrogenase (H6PD) (*2*). This enzyme represents the unique reticular source of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) moieties needed for cortisone activation (*3,4*) in the same endoplasmic reticulum by 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1). In this line, the increased use of NADPH reductive power caused by the administration of pharmacologic cortisone doses might "transiently" increase H6PD activity and thus myocardial ^{18}F-FDG uptake. However, this variable should have played a minor role in our main observation (*5*) for the following reasons.

First, in our experimental animal model, in which steroids were not administered, DXR dose-dependently increased myocardial ^{18}F-FDG accumulation. Second, as suggested by Finessi et al. in their previous study (*6*), the extra-steroid administration might be a strong, independent thought "transient" variable able to affect myocardial ^{18}F-FDG accumulation. However, in our retrospective analysis, left-ventricular (LV) SUV was significantly increased in DXR-treated patients with respect to controls at the third PET study but remained persistently elevated 6 mo after chemotherapy (and eventually extra-steroid) discontinuation. Finally, and more importantly, when we focused on adriamycin, bleomycin, vincristine, dacarbazine–treated patients who accepted to undergo a later clinical evaluation, the occurrence of DXR-induced cardiotoxicity was significantly related to lower values of LV-SUV at baseline, in which patients did not received any therapy.

Altogether these observations seem to indicate that whatever its degree, the effect of cortisone therapy should have been transient and independent from baseline condition.

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Staging, Restaging, and Treatment Response Assessment in Lymphomas: What We Should Know

TO THE EDITOR: We read with interest the review published by Jadvar and colleagues (*1*) who highlight the main indications of ^{18}F-FDG PET/CT for restaging and treatment response assessment in oncology. They point out its clinical impact in 7 of the most commons cancers. However, we think it is necessary to give additional information on the role of ^{18}F-FDG PET/CT in lymphomas and to draw the attention of the readers to the most relevant papers in the field. Indeed, on the basis of the results of important studies, PET/CT has changed the management of many subtypes of lymphoma and we would like herein to address some key points.

Lymphomas are a heterogeneous group of tumors encompassing numerous entities with different prognosis and treatment. Lymphomas were usually classified as ^{18}F-FDG–avid or nonavid, depending of their subtypes. The role of ^{18}F-FDG PET/CT, initially limited to some of the ^{18}F-FDG–avid subtypes (Hodgkin lymphoma [HL], diffuse large B cell [DLBCL], and follicular lymphomas), is now recognized for the clear majority of lymphomas and has been recently demonstrated for T cell lymphoma, mantle cell lymphoma, and plasmablastic lymphomas. It should be emphasized that, among the main roles of ^{18}F-FDG PET/CT at staging, PET is now recommended as a noninvasive technique for the detection of bone marrow involvement in HL and DLBCL and has replaced the invasive bone marrow biopsy in HL and in some cases in DLBCL (*2*). This recommendation has improved the quality of a patient's life. The second point is the role of ^{18}F-FDG PET/CT in follicular lymphoma, where it has shown capabilities (*3*) in identifying the tumor site of transformation and guiding biopsy for diagnosis. For staging, it is important to underline that for the ^{18}F-FDG–avid lymphoma there is no more proven advantage than to perform separate contrast-enhanced CT because ^{18}F-FDG PET/CT has a much better sensitivity.

Excellent general reviews and consensus papers have documented the indications of ^{18}F-FDG PET/CT according to each clinical challenge for each subtype of lymphoma. Therefore, we will mainly focus on the response assessment to treatment and will report on the main studies demonstrating the usefulness of interim PET–guided therapy.

Lymphomas are certainly the oncologic application for which ^{18}F-FDG PET/CT provided the most significant improvement compared with conventional imaging. ^{18}F-FDG PET/CT allows a better identification of treatment failure and identifies patients who are deemed to benefit from salvage therapy. This evaluation at the end of the first line of treatment has been standardized on the basis of a Deauville 5-point scale and more recently reshaped in the Lugano classification (*2*). Compared with conventional imaging, ^{18}F-FDG PET/CT provides a more reliable evaluation (removing the CT unconfirmed responses) and a better specificity in response evaluation, and leads to a more accurate identification of nonresponder patients with a strong prognostic impact. This high clinical value has been documented in large series for the main common lymphomas such as HL, DLBCL, and follicular lymphoma and was also validated in cost-effectiveness studies (*4–6*).

Large prospective trials, especially in HL, have shown that an early evaluation of treatment response using interim PET/CT after 2 cycles of chemotherapy (PET2) could be used to adapt treatment strategy. The H10 trial for early-stage HLs has shown that PET-driven chemointensification (adriamycin, bleomycin, vincristine, dacarbazine [ABVD] to BEACOPP regimen) of PET2-positive patients significantly enhances the progression-free survival (*7*). Similar data have been shown for advanced HL in several trials in which interim PET2–negative patients followed the initial ABVD treatment whereas the therapy regimen for PET2-positive patients was intensified with BEACOPP (*8*). This interim PET–personalized