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# Doxorubicin Effect on Myocardial Metabolism as a Prerequisite for Subsequent Development of Cardiac Toxicity: are there unsuspecting confounders?

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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). They assessed the role of $^{18}$F-FDG PET/CT in the prediction of doxorubicin cardiac toxicity in 69 patients treated with chemotherapy regimen for Hodgkin Lymphoma (HL); furthermore they investigated the possible dose-dependent nature of doxorubicin toxicity in 15 athymic mice and they concluded that in patients undergoing doxorubicin administration, not only myocardial $^{18}$F-FDG uptake is 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 down-regulation 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 pre-clinical studies, some already cited by Bauckneht et al. (4,5), suggest the opportunity of investigate the correlation between changes in myocardial $^{18}$F-FDG uptake in pre- and post-chemotherapy 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 treated with chemotherapy some elements may modify the variable avidity for glucose (9) and shift the myocardial metabolism from beta oxidation of fatty acids to glycolysis, also taking into account the possible role of steroids (for iatrogenic hyperglycaemia) and granulocyte colony stimulating factor (for insuline-like effects). We tested our hypothesis retrospectively in a group of patients (n=24) treated with a regimen of Adriamycine, Bleomycine, Vincristine, Dacarbazine (ABVD) plus 20mg Desametasone with HL, excluding patients with antecedent cardiovascular disease, diabetes and previous chemotherapy or

mediastinal irradiation and identifying 10 patients that received from 50 to 575 mg of steroids extra from the standard (extra-steroids group).

All patients underwent $^{18}$F-FDG PET/CT at staging, interim and final evaluation respectively: 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 Maximum Standardized Uptake Value (SUVmax) 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, indipendent (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 an useful biomarker of cardiac toxicity, but first clarifying the role of other factors that may concur as confounders in $^{18}$F-FDG uptake, such as steroids administration.

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