Journal of Nuclear Medicine, published on January 18, 2018 as doi:10.2967/jnumed.117.206797

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

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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 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 FDG uptake (1).

On the other hand, the relevance of corticosteroids nicely fits with our hypothesis about the existence of a peculiar 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 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 pharmacological cortisone doses might “transiently”, increase H6PD activity and thus myocardial FDG uptake. However, this variable should have played a minor role in our main observation (5) for the following reasons.

Firstly, in our experimental animal model, in which steroids were not administered, DXR dose-dependently increased myocardial FDG accumulation. Secondly, 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 FDG accumulation. However, in our retrospective analysis, LV-SUV was significantly increased

in DXR treated patients with respect to controls at PET3 but remained persistently elevated 6 months after chemotherapy (and eventually extra-steroids) discontinuation. Finally, and more importantly, when we focused on ABVD-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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