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Blood-based dosimetry in radiopeptide therapy patients using the DSB focus assay

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Objectives: The aim of the study is to investigate DNA double strand break (DSB) formation as a function of the absorbed dose to the blood using foci staining (γ-H2AX foci co-localized with 53BP1 foci) of blood lymphocytes in patients after their first radiopeptide therapy with Lu-177-labelled DOTATATE/-TOC, and to compare this approach to an *in-vitro* calibration curve. Methods: We investigated 16 patients during their first treatment with 7.2±0.4GBq. At least 6 peripheral blood samples were obtained before, and between 0.5h and 48h post administration (minimum 3 samples within the first 4 hours). Whole body activity retention was determined combining external dose rate measurements and whole body gamma camera scans. The absorbed dose to the blood was calculated in analogy to the EANM DTC Dosimetry SOP. The average frequencies of radiation-induced foci (RIF) containing both γ-H2AX and 53BP1 fluorescence were derived from mononuclear lymphocytes isolated from peripheral blood samples by density centrifugation of CPT tubes, followed by two-colour immunofluorescence γ-H2AX and 53BP1 staining. The foci containing both DSB markers were inspected manually in a fluorescence microscope equipped with a red/green double-band-pass filter by an experienced observer. The average number of RIF/nucleus as a function of the absorbed dose to the blood were analysed and compared to an *in-vitro* calibration curve established in our lab using I-131 and Lu-177. Results: The mean absorbed dose to the blood in the patients was 27±12mGy at t=2h, 40±19mGy at t=4h, 72±27mGy at t=24h, 86±26mGy at 48h, and 134±44mGy total absorbed dose. A linear fit from 0h-4h as a function of the absorbed dose to the blood was in agreement with our *in-vitro* calibration curve. However, the correlation was less than 40% due to individual variation in some patients leading to substantial deviations. At later time points a linear relationship with the absorbed dose was no longer observed in accordance with the diminishing dose rate and progression of DSB repair in the patients' blood cells. Still, there was an elevated number of RIF/nucleus detectable in the samples taken at the more advanced time points (≥24h). Conclusions: Measurements of RIF and the absorbed dose to the blood after administration of Lu-177 may be used to obtain data on the individual dose-response relationships after nuclide incorporation *in-vivo*. Further analysis of the DSB repair kinetics, the clinical dose response, and the disease stage of the patients is needed for identifying reasons for patient-specific variations.