Induction and repair of DNA double-strand breaks in blood leukocytes of prostate cancer patients during Lu-177-PSMA therapy

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Abstract

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Objectives: Despite the increasing number of therapies with Lu-177-PSMA, radiation-induced DNA damage in blood leukocytes of prostate cancer patients undergoing this treatment has not been investigated yet. Therefore, the aim of our study was to use the γ-H2AX+53BP1 focus assay combined with internal dosimetry to analyze the time- and absorbed dose-dependency of DNA double-strand break (DSB) induction and repair in peripheral blood leukocytes of prostate cancer patients during therapy with Lu-177-PSMA.

Methods: 16 prostate cancer patients receiving their first treatment with Lu-177-PSMA were included in the study. Blood samples were taken before and nominally 1 h, 2 h, 3 h, 4 h, 24 h, 48 h and 96 h after administration. An aliquot of each blood sample was measured in a calibrated, high-purity germanium detector, while another aliquot was prepared for immunofluorescent staining with γ-H2AX and 53BP1 antibodies. For DSB quantification, co-localizing γ-H2AX+53BP1 foci were counted manually in 100 cells per sample. Additionally, 7-8 external dose rate measurements and 3-4 gamma camera scans were performed to determine the whole body activity retention. Integrated time-activity curves of the blood and the whole body were used to calculate the absorbed doses to the blood as described in [1].

Results: The mean absorbed dose to the blood 4 h after administration was (40 ± 9) mGy. More than 80% of the mean total absorbed dose to the blood, which was (109 ± 28) mGy, was reached at the last sampling time point 96 h after administration for all patients except one. Within the first four hours after administration, the average number of radiation-induced foci (RIF) per cell increased. 1 h after administration the average number of RIF per cell was (0.29 ± 0.14), 4 h after administration it was (0.38 ± 0.17). This increase correlated linearly with the absorbed dose to the blood during the first 2.6 h, which is in accordance with a previously published *in-vitro* calibration curve [2]. After four hours, the average number of RIF decreased due to DSB repair and decreasing absorbed dose rates. In some patients, RIF were still detectable even 96 h after administration. In most patients, however, DSBs were repaired effectively. For the last two time points, there was a linear correlation between the number of RIF and the absorbed dose rate. Furthermore, we observed a significant correlation between the PSA level of the patients and the absorbed dose rate at the last sampling time point. To describe the time-dependency of the RIF, we established a model including a linear absorbed dose-dependent increase and a bi-exponential decay representing DSB repair.

Conclusions: In general, we observed a pattern of the time- and absorbed dose-dependent induction and repair of DSB foci during Lu-177-PSMA therapy that is similar to that of other radionuclide therapies [1, 3]. The correlation with clinical findings needs further research in a larger number of patients.
References: 1. Eberlein U, Nowak C, Bluemel C et al., Eur J Nucl Med Mol Imaging. 2015;42(11):1739-49. doi:10.1007/s00259-015-3083-9 . 2. Eberlein U, Peper M, Fernandez M et al., PLoS One. 2015;10(4):e0123174. doi:10.1371/journal.pone.0123174 . 3. Eberlein U, Scherthan H, Bluemel C et al., J Nucl Med. 2016;57(2):173-9. doi:10.2967/jnumed.115.164814 .