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Radiobiology of targeted radionuclide therapy to enhance treatment effects

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Radiobiological principles of external beam- and brachy radiotherapy have been studied for decades, while the radiobiology of radionuclide therapy is still in its infancy. During peptide receptor radionuclide therapy (PRRT) of metastasized neuroendocrine tumors (NETs) with overexpression of somatostatin receptors (SSTR2), Lutetium-177 is targeted to the tumor via coupling to the somatostatin analogue DOTA-[Tyr3]octreotate (177Lu-DOTA-TATE), that has high affinity to SSTR2. Lutetium-177's β-particles (mean energy 0.133MeV) will induce DNA damage leading to tumor cell death with limited harm to healthy tissues. Patient treatment strongly increases progression-free survival and life quality. There is nevertheless still room for improvement, as very few patients are cured at this stage of disease. For possible future therapy optimizations, it is essential to have a better understanding of local treatment effects, both in tumor and healthy tissues. To gain insight in the underlying radiobiological principles, we characterized the PRRT-induced DNA damage response (DDR) in cell lines, ex vivo cultured human NET slices and xenografted mice. PRRT induces DNA double strand break (DSBs) which are repaired over time. Our results show that DDR inhibitors (PARPi, DNA-PKi and ATMi) differentially impair DNA repair (radiosensitizers) and vastly increase cell death in SSTR2-positive cells and NET slices, while SSTR-negative cells are not sensitized to PRRT. Furthermore, xenografted mice were followed for 14 days post PRRT and scanned with SPECT/MRI. Dosimetric calculations were performed based on both in vivo imaging and ex vivo biodistribution data. Our analyses show that PRRT produced DSBs in the tumor and dose limiting organs; the kidneys and bone marrow. DSBs in the tumor (dose 10.5Gy over 14days) were observed until at least 14days post treatment (also massive apoptosis induction), while DSBs in the bone marrow and kidneys (dose 3.7Gy over 14days) were only observed transiently until 2 days after treatment, illustrating the window of opportunity for combination therapy with DDR inhibitors.

Biography

Julie Nonnekens completed her PhD in molecular oncology at the University of Toulouse, France in 2013. She pursued Postdoctoral studies at the Hubrecht Institute and Erasmus MC in the Netherlands and is now an assistant professor at the Erasmus MC. Her research focusses on the radiobiology of targeted radionuclide therapy and is published in high-ranking journals. Furthermore, Julie was awarded two young investigator awards and obtained various grants to continue her research.

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