Nanovectorized radiotherapy by convection-enhanced delivery (CED), a promising strategy that demonstrates high efficacy in a murine model of human endometrial adenocarcinoma

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Résumé en anglais	Aim: To evaluate the biodistribution, the toxicity, the dosimetry and the antitumor efficacy of intra-tumoral injection of rhenium-188 loaded nanoparticles (LNC-188Re-SSS) by CED. Materials and methods: Ishikawa endometrial carcinoma cell lines were implanted subcutaneously in nude mice (n=70). For biodistribution and efficacy studies CED procedure was realized at D28 after tumour implantation. CED was performed using an osmotic pump (0.5µL/min for 20 minutes) after immobilisation of anaesthetized mice on a stereotactic frame. For biodistribution studies, animals (n=30) were injected by CED either with 3MBq of 188ReO4- (n=15) or LNC-188Re-SSS (n=15) and sacrificed at 1h (n=10), 24h (n=10) or 72h (n=10). For efficacy studies, control group mice were injected by CED with saline (n=8) or blank LNC (n=8) and treated group mice were injected with escalating dose of LNC-188Re-SSS: 3MBq (n=8), 6 MBq (n=8) or 12 MBq (n=8). Efficacy on tumour growth was assessed by clinical palpation and µMRI. The time for the tumour volume doubling was chosen as endpoint, leading to the euthanasia of the animal. The physical dose deposited in the tumour for each treated animal was estimated by Monte Carlo simulation (Geant4) using measured biodistribution and µMRI tumour volumes,. Haematological toxicity in mice was evaluated using blood sampling of 50µL (retro-orbital sinus) at D2, D7, D14 and D21 after treatment with saline (n=4) and after treatment with LNC-188Re-SSS, 3MBq (n=4), 6 MBq (n=4) or 12 MBq (n=4). Results: Nanovectorization of 188Re combined with CED allowed the confinement of more than 30 % of ID in the tumour limiting therefore urinary excretion of 188Re since 0,1% versus 81,9% of ID were excreted in urine 24h after CED of LNC-188Re-SSS and 188ReO4- respectively (p=0.016). Nanovectorized radiotherapy has drastically increased the median survival time compared with control group. Animals whose tumor received a dose higher than 69 Gy (69-340 Gy) showed an ISTmedian of + 933%, whereas animals whose tumor received a dose lower than 69 Gy (21-67Gy) showed an ISTmedian of + 391%. Complete response with eradication of the tumor was observed in 4/12 (33.3%) animals of the former group. Depletion of platelets was observed following LNC-188Re-SSS injection with a time to nadir between D14-D21 whereas transient lymphocyte depletion was only observed at D7 for the highest administered activities (12MBq). Conclusion: CED of LNC-188Re-SSS demonstrates interesting biodistribution properties and high efficacy in a model of human endometrial carcinoma.
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