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Safety and therapeutic efficacy of 225Ac-DOTA-Substance P for therapy of brain tumors

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Glioblastoma multiforme (GBM) is the most common, aggressive and devastating malignant primary brain tumor in humans. Treatment options for recurrent glioblastoma multiforme (GBM) are very limited. For many years, no significant progress in the treatment of tumors was monitored. Local treatment with radiopharmaceuticals is a promising method of treatment. GBM cells express high levels of the GPCR neurokinin type 1 receptor (NK-1R) and modified substance P can be used as its ligand for tumor cell targeting. Targeted alpha therapy with DOTA-Substance P (SP) labeled with the short range alpha emitter allows for selective irradiation and killing of tumor cells. In the first step 213Bi with a short half-time (45 min) was used for labeling of SP and local injection to the tumor and promising results were described. It seems that this radioisotope can be use in treatment of small tumors. The relatievly short half-live of 213Bi and a slow diffusion process limit the optimal distribution of the tracer in the larger tumors. A radioisotope with longer half time might be preferred in this group of patients. Therefore 225Ac with a half live of 9.9 days has been applied. 21 patients with histologically confirmed recurrence of the glia tumor grade II-IV were included in the study: grade II - 1 patient, grade III, - 8 patients. grade IV -12 patients. All patients received standard treatment (surgery + radio-chemo-therapy). When recurrence of disease was diagnosed, resection of the tumor and implantation of the cat-cap system intratumoral or to the postsurgical cavity were performed. Few weeks later 20-40 MBq 225Ac-DOTA-SP was given. 68Ga-DOTA-Substance P (68Ga-DOTA-SP) was co-injected with 225Ac-DOTA-SP to assess biodistribution using PET/CT. Therapeutic response was monitored with performance status and MRI imaging. In the group of patients with primary glioblastoma multiforme (grade IV) PFS was 4-112 weeks; OS from primary diagnosis was 32-128 weeks; OS from recurrence was 28-62 weeks; and OS from radioisotopic treatment was 8-48 weeks.
Intracavitary / intratumoral injection of 225Ac-substance P was well tolerated. Only mild, temporary adverse effects observed (edema, epileptic seizures, aphasia). Patient recruitment and dose escalation is ongoing.

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