Therapeutic efficacy and toxicity of 225Ac-labelled vs. 213Bi-labelled tumour-homing peptides in a preclinical mouse model of peritoneal carcinomatosis.

Abstract:
Targeted delivery of alpha-particle-emitting radionuclides is a promising novel option in cancer therapy. We generated stable conjugates of the vascular tumour-homing peptide F3 both with (225)Ac and (213)Bi that specifically bind to nucleolin on the surface of proliferating tumour cells. The aim of our study was to determine the therapeutic efficacy of (225)Ac-DOTA-F3 in comparison with that of (213)Bi-DTPA-F3. ID(50) values of (213)Bi-DTPA-F3 and (225)Ac-DOTA-F3 were determined via clonogenic assays. The therapeutic efficacy of both constructs was assayed by repeated treatment of mice bearing intraperitoneal MDA-MB-435 xenograft tumours. Therapy was monitored by bioluminescence imaging. Nephrotoxic effects were analysed by histology. ID(50) values of (213)Bi-DTPA-F3 and (225)Ac-DOTA-F3 were 53 kBq/ml and 67 Bq/ml, respectively. The median survival of control mice treated with phosphate-buffered saline was 60 days after intraperitoneal inoculation of 1 × 10(7) MDA-MB-435 cells. Therapy with 6 × 1.85 kBq of (225)Ac-DOTA-F3 or 6 × 1.85 MBq of (213)Bi-DTPA-F3 prolonged median survival to 95 days and 97 days, respectively. While F3 labelled with short-lived (213)Bi (t 1/2 46 min)
reduced the tumour mass at early time-points up to 30 days after treatment, the antitumour effect of (225)Ac-DOTA-F3 (t (1/2) 10 days) increased at later time-points. The difference in the fraction of necrotic cells after treatment with (225)Ac-DOTA-F3 (43%) and with (213)Bi-DTPA-F3 (36%) was not significant. Though histological analysis of kidney samples revealed acute tubular necrosis and tubular oedema in 10-30% of animals after treatment with (225)Ac-DOTA-F3 or (213)Bi-DTPA-F3, protein casts were negligible (2%), indicating only minor damage to the kidney. Therapy with both (225)Ac-DOTA-F3 and (213)Bi-DTPA-F3 increased survival of mice with peritoneal carcinomatosis. Mild renal toxicity of both constructs favours future therapeutic application.