Fractionated locoregional low-dose radioimmunotherapy improves survival in a mouse model of diffuse-type gastric cancer using a 213Bi-conjugated monoclonal antibody.

**Abstract:**

PURPOSE: Locoregional radioimmunotherapy of i.p. tumor cell dissemination of diffuse-type gastric cancer using the alpha-emitter 213Bi displayed good therapeutic results after a single application depending on the time interval between tumor cell inoculation and injection of the 213Bi-immunoconjugate. The aim of the present study was to compare single versus double i.p. injection of a tumor-specific antibody (d9MAb) conjugated with low activities of 213Bi in terms of therapeutic efficacy and toxicity. EXPERIMENTAL DESIGN: Nude mice were inoculated i.p. with 1 x 10^7 human gastric cancer cells (HSC45-M2) expressing tumor-specific mutant d9-E-cadherin (d9-E-cad). After tumor cell inoculation, the mice were injected i.p. with a single injection at day 1 or 8, or double injections at days 1 and 8 or days 8 and 15 with 0.37, 0.74, or 1.48 MBq 213Bi-d9MAb. Therapeutic efficacy was determined by median survival, and toxicity was evaluated by leukocyte and platelet counts. The development of i.p. carcinomatosis was monitored by carcinoembryonic antigen concentrations in the serum of the mice. RESULTS: The median survival of treated animals increased, depending on the time interval (days) between tumor cell inoculation and therapy, and the injected activity, from 22 days of untreated mice to 48 days...
(0.37 MBq, 1 day), 84 days (0.37 MBq, 1 and 8 days), 37 days (0.37 MBq, 8 days), 46 days (0.37 MBq, 8 and 15 days), 42 days (0.74 MBq, 8 days), 78 days (0.74 MBq, 8 and 15 days), and 44 days (1.48 MBq, 8 days). The injected activities did not reduce leukocyte and platelet counts. Carcinoembryonic antigen, which was not detectable in the serum of tumor-free mice, increased after tumor cell inoculation and tumor proliferation and decreased after each therapeutic application of 213Bi-d9MAb. CONCLUSIONS: Double application of only 0.37 MBq of 213Bi-d9MAb at days 1 and 8 after tumor cell inoculation significantly prolonged median survival in nude mice suffering from i.p. tumor cell dissemination compared with a single injection. Even in an advanced stage of the disease, double injection of 0.74 MBq at days 8 and 15 was superior to a single injection of 1.48 MBq at day 8 without any sign of toxicity.