Abstract:

PURPOSE: The locoregional application of tumor-specific antibodies conjugated with highly cytotoxic alpha-emitters is a promising new strategy for therapy of i.p. tumor cell dissemination. Using this approach, an antibody specifically targeting diffuse-type gastric cancer cells was coupled to the high linear energy transfer alpha-emitter (213)Bi for treatment of i.p. tumor cell spread in a nude mouse model.

EXPERIMENTAL DESIGN: Nude mice were inoculated with HSC45-M2 human gastric cancer cells expressing mutant d9-E-cadherin. Twenty-four h after cell inoculation, mice received i.p. injections of either (213)Bi-d9MAb specifically binding to mutant d9-E-cadherin of HSC45-M2 cells or unspecific (213)Bi-d8MAb (7.4 or 22.2 MBq). Survival of treated animals was monitored compared with controls that had been injected with nonlabeled monoclonal antibody (MAb) or saline. Toxicity was evaluated by WBC counts after injection of 1.85, 7.4, or 22.2 MBq and analysis of chromosomal aberrations of bone marrow cells after injection of 7.4, 14.8, or 22.2 MBq. RESULTS: Survival rates of control mice and of mice treated with (213)Bi-MAbs differed significantly: the mean survival of untreated controls and mice that were given the nonlabeled

antibody was 23 and 26 days. After injection of 22.2 MBq of the specific (213)Bi-d9MAb or the unspecific (213)Bi-d8MAb, mean survival was at least 143 or 130 days, respectively. Treatment with 7.4 MBq of (213)Bi-d9MAb increased mean survival to at least 232 days and with (213)Bi-d8MAb to at least 172 days. WBC counts decreased within 2 days after (213)Bi-therapy but reached pretreatment values between day 14 and 21 after activity injection. Chromosomal aberrations in bone marrow cells could only be detected at day 1 after (213)Bi-therapy. The frequency of chromosomal damages increased depending on the applied (213)Bi-activity. CONCLUSIONS: The therapeutic efficacy of the (213)Bi-d9MAb together with a low bone marrow toxicity support the locoregional therapy for that subgroup of diffuse-type gastric carcinoma patients expressing d9-E-cadherin.