Experimental radioimmunotherapy of ovarian cancer

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The therapeutic efficacy of ^{131}I-MAb A18 with respect to stage (i.e. minimal disease vs. nodules of different size) and route of administration (i.e. intravenously vs. intraperitoneally) was tested in nude mice with IGROV1 ovarian carcinoma (intraperitoneally). We tested MAb distribution by autoradiography, dose distribution by TLD implantation, and the therapeutic effect by following the survival of mice. As previously reported by other groups, small tumour lesions were most effectively targeted by intraperitoneal application, while large nodules were mainly accessible to blood-borne MAb. A selectivity index (specific:non-specific MAb) of 15.8 vs. 2.9 was found in small vs. large nodules after intraperitoneal injection, while intravenous values were 5.2 and 4.8, respectively. The moderate advantage of intravenous injections did not entail a measurable therapeutic effect in animals with large intraperitoneal nodules. Survival could be markedly increased by intraperitoneal injection of 20 MBq into animals with minimal disease, i.e. from 9 days and 11 days (mean survival time, cold and hot non-specific MAb, respectively) to 23 days (specific MAb). Radiation dose estimates were variable because of substantial *de novo* growth of (non-accumulating) tumour tissue around implanted TLD probes.

Lymphoscintigraphy using radiolabelled epidermal growth factor (EGF) as a tumour-seeking agent in cervical cancer

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EGF receptors are expressed in large quantities on the surface of squamous cell carcinomas such as carcinomas of the uterine cervix. Therefore EGF should serve as an ideal "specific" tumour-seeking agent. The aim of our study was to evaluate the possibility of lymph node metastases detection in cervical cancer. Eleven patients with cervical cancer, all planned for primary irradiation therapy, were investigated by lymphoscintigraphy using radiolabelled recombinant EGF as tumour-seeking agent. The patients were selected because of their high probability of having lymph node metastases. ^{123}I labelled EGF was injected subcutaneously into the web space of both feet. All patients were injected with 50 μg EGF labelled with 500 uCi per side. Scintigrams were taken in short predefined intervals up to 24 h pi. Wherever possible, scans were compared with computed tomography, ultrasound, clinical investigation and in one case with needle biopsy. In 7 out of the 11 investigated patients selective accumulation in primary and secondary tumour sites was obtained.

Radiolocalisation of tumour pretargetted by biotinylated monoclonal antibody

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We describe (a) two steps and (b) three step strategies to label Mabs *in vivo*.

(a) Nine patients with ovarian carcinoma, 6 with documented lesions and 3 with no evidence of disease (NED) were injected intraperitoneally with 2 mg of biotinylated Mab Mov18, followed 3–5 days later by 100–150 μg of ^{111}In labelled streptavidin (380 MBq/mg) in 500 ml of normal saline. 5 patients with documented lesions had positive scans. Out of 3 NED patients, 2 had negative scans and 1 had a hot spot in the pelvis. All patients underwent surgery 3–7 days after scanning. Resected tumours and normal tissues were counted for dosimetry calculations. Injected dose per gram of tumour was on average 0.2 + 0.1%. Over 24 h 17% id was found in the urine, 8% in the blood, and 60% in the peritoneal cavity.

(b) The anti-CEA Mab F023C5 was biotinylated and 1 mg was administered intravenously in 10 patients with documented CEA positive tumours. After 3 days, 4 mg of cold avidin was injected followed 48 h later by 200–500 μg biotin labelled with ^{111}In (2–3 mCi). Blood clearance of ^{111}In biotin had a multiexponential curve with a fast component of T1/2 of 5 ± 3 min. The urinary excretion of radioactivity over 2 h was 58 ± 5% of injected dose. Tumours and metastases (including liver secondaries) were detected in all patients within 3 h postradioactivity administration on both planar and SPECT imaging. Tumour to blood ratio was 2.4 ± 2 and tumour to liver ratio 2.5 ± 0.1 at 90 min after injection. One patient developed a human anti-streptavidin immune response and 4 patients developed a human anti-avidin response.

Two-phase radioimmunotherapy using bispecific MAbs (bsMAbs)

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We previously demonstrated that repetitive intravenous injections (10 × 250 μg) of high doses of CEA- or GIT-mucin specific MAbs (BW 431 and BW 494) can result in a homogeneous penetration by antibody of pancreatic and colon carcinoma xenografts in nude mice and prolonged retention of MAb in the interstitial space and on carcinoma cells (>20 days after administration). In contrast, 10 days after antibody administration no MAb could be found in normal tissues. These observations indicate that an optimal tumour therapeutic effect might be obtained if a non-toxic localisation and tumour penetration phase of a bs MAb (anti CEA × anti EDTA-Y-90) is followed by a fast specific binding (whole body half-life 30') of a toxic B-emitting EDTA-Y-90 complex. To realise this, bs MABs selective for CEA- and EDTA-Y-90 or GIT-mucin and EDTA-Y-90 were generated using quadroma technology. Bs MABs were isolated from quandroma supernatants by immuno-affinity chromatography on two consecutive sepharose columns coated with anti-idiotypic MAbs. The binding and storage potential of these highly purified bs MAb preparations in nude mouse xenografts and their efficiency to capture and retain the ETDA-Y-90 molecule at the tumour site has been achieved.

Comparison of imaging and therapeutic efficacy of two bifunctional monoclonal antibody delivery systems

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Imaging and dosimetry studies were undertaken utilising two different bifunctional antibodies (BFA) in a unique isotope delivery system. For each BFA delivery system, two murine F(ab') fragments of differing specificity were chemically linked to form $F(ab')_2$ (ZCE/CHA and CEM/CHA). One F(ab') is reactive with CEA (CEM-231 or ZCE/CHA and CEM/CHA), and the other with ^{111}In benzyl EDTA (CHA-255). The system is administered in two intravenous injections—a 20 mg pre-localisation dose of BFA, followed in 24–120 h by carrier BFA (0.1 mg–0.5 mg) combined with EOTUBE, an ^{111}In hydroxyethyl-thiourea-benzyl-EDTA. Blood and urine kinetics were measured and planar scans of selected areas were done. Tumour and normal tissue levels were calculated. For comparison of the two BFAs, we reviewed patients (CEM/CHA n = 13, ZCE/-CHA n = 13) receiving a 20 mg pre-localised injection of BFA followed in 96 h by injection of carrier BFA with EOTUBE. 95% of known lesions were targetted with ZCE/CHA as opposed to 40% with CEM/CHA. Tumour doses as high as 86% Gy were seen with ZCE/CHA and only 16 Gy with CEM/CHA. ZCE/CHA demonstrated better imaging sensitivity. However, lower marrow concentrations were seen with CEM/CHA. This BFA system demonstrates the potential for delivering to tumour a variety of imaging and therapeutic agents.