Session 6. Chairman: S. Matzku, Heidelberg, FRG

Diagnostic applications of radiolabelled monoclonal antibodies

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The use of radiolabelled murine monoclonal antibodies (MAb) has proven to be a reliable method for the diagnosis of recurrent (primary), metastatic, and occult tumours over the last decade. Our clinical experience since 1984 extends to the use of 18 different MAb labelled with ^{131}I, ^{111}In and ^{99m}Tc in more than 1000 patients with various solid tumours—GI tract (mainly colon cancers), ovarian and breast carcinoma, bladder cancer, neuroblastoma, germ cell tumours and others. Regarding immunoscintigraphy as a clinical entity, the most important oncological indications are (1) colorectal cancer recurrences in patients with rising serum CEA after curative resection of the primary tumour and otherwise normal diagnostic workup (sensitivity >70%, specificity >90%); (2) ovarian cancer (diagnostic accuracy about 82%) and diagnosis/staging before SLO/primary tumour operation; and (3) bladder carcinoma detection of extravesical LN-metastases/staging (diagnostic accuracy >85%).

Enhancing tumour dose via improved antibody radiohalogenation methods and alpha-emitting ^{211}At

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Loss of radiolabel from monoclonal antibodies (MAbs) *in vivo* is a factor contributing to the low tumour radiation absorbed doses reported in clinical studies. To obviate this problem for halogen nuclides, we have developed an approach for MAb labelling utilising N-succinimidyl-3-(alkylstannyl)benzoate (ATE) intermediates. Use of ATE to label 81C6 IgG, a MAb reactive with human gliomas, with ^{131}I resulted in a thyroid uptake (an indicator of dehalogenation) of ≤0.1% of the injected dose and increased cumulative radiation dose to subcutaneous xenografts by more than 3-fold compared to MAb labelled using iodogen. The $F(ab')_2$ fragment of Mel-14, also reactive with gliomas, was labelled with both ^{131}I and ^{211}At using ATE. Since ^{211}At is an alpha emitter, it offers the advantages associated with LET radiation. 3 to 24 h after injection, uptake of ^{131}I (9.7 ± 2.1–14.2 ± 3.3% ID/g) and ^{211}At (8.7 ± 2.1–14.7 ± 1.2% ID/g) in D-54 MG glioma xenografts was similar and 2- to 3-fold higher than previously reported for Mel-14 $F(ab')_2$ labelled using iodogen. For ^{131}I, labelled $F(ab')_2$ tumour:tissue ratios using ATE at 24 h were comparable to those obtained with iodogen at 120 h; however, since tumour uptake with ATE at 24 h (12.8 ± 2.8% ID/g) was about 30 times greater than with iodogen at 120 h, use of the ATE method could permit increased tumour dose deposition without decreasing the therapeutic index.

Dose to tumour and normal tissues from ip administered ^{90}Y, ^{211}At or ^{131}I labelled monoclonal antibodies

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Doses to normal tissues and tumour from intraperitoneally administered radiolabelled antibodies have been calculated for ^{90}Y, ^{131}I and ^{211}At. The dose calculations utilise data on the specific activity of intraperitoneal fluid administered, the percent injected dose/gm uptake by tumour, and a model for diffusion of antibody/radionuclide complex into peritoneal tissues. Calculations are performed for planar and hemispherical tumour shapes, ranging in size to establish the influence of geometry on dose distribution. In addition, calculations on tumours obtained from biopsies have also been performed. For the conditions simulated, these studies show that the surface dose to tumour for ^{90}Y is approximately 60Gy from a 20 mCi administration in 1500 ml of fluid, and the dose falls rapidly to 50% within 1 mm. The surface dose from ^{131}I (130 mCi) is 240 Gy and falls to 20Gy by 0.05 cm while the surface dose for an administration of 70 mCi of ^{211}At is initially 450 Gy and falls to 50% in 30 microns. Both surface geometry and tumour size are important factors in the uniformity of dose to tumour, as is the dose administered, uptake, distribution, and residence time factors. This model is applied to tumour geometry obtained from biopsies. Results suggest that even with ^{90}Y, intraperitoneal radioimmunotherapy is most suited for lesions of 1–2 mm depth for a minimum total dose of 20 Gy.

Anti-idiotypes in cancer immunotherapy

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The immunomodulatory role of anti-idiotypic antibodies (Ab2) in patients with gastrointestinal cancer has been demonstrated in two types of clinical trials. In the first, patients were treated with a monoclonal antibody CO17-1A (Ab1) defining a 30/40 kDa gastrointestinal carcinoma-associated antigen. Ab1 administration initiated an idiotypic cascade as demonstrated by the induction of both Ab2 and anti-anti-idiotypic antibodies (Ab3) in the treated patients. The Ab2 were directed against the antigen-combining site of Ab1 and therefore may bear the internal image of the antigen defined by Ab1. The Ab3 bound to tumour cells and isolated tumour antigen with the same specificity as the Ab1 at the beginning of the idiotypic cascade. A beneficial role of the Ab3 is postulated for patients showing delayed clinical responses to Ab1 therapy. In another trial, patients with advanced colorectal cancer responded to immunisation with polyclonal goat Ab2 that functionally mimicked *in vitro* and *in vivo* (animals) the CO17-1A antigen by developing highly specific Ab3 with anti-tumour binding reactivities. The Ab3 competed with Ab1 for binding to the same epitope. The Ab3 responses may underlie the clinical responses observed in some of the Ab2-treated patients. Thus, Ab2 are promising agents in immunotherapy approaches to cancer. Recently, mono-clonal Ab2 have been developed against Ab1 CO17-1A in rats. In preclinical studies, the monoclonal Ab2s were superior to the polyclonal goat Ab2 in their capacity to induce antigen-specific Ab3. Monoclonal Ab2s therefore are candidates for treatment of patients with cancer.

Idiotypic immunotherapy of cancer

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Tumours may grow because they are not recognised by the immune system or because the immune system is specifically suppressed. Immunisation with a monoclonal anti-idiotypic antibody which mimics a tumour antigen may overcome this tolerance/suppression. A human monoclonal antibody which recognises the idiotypic region of the mouse anti-tumour monoclonal antibody 791T/36 has been produced. It induces both cellular and humoral xenogeneic immune responses to tumour cells in experimental animals. It may therefore stimulate similar responses in patients with cancer. However, to test if syngeneic anti-idiopathic responses can be stimulated, a mouse monoclonal antibody recognising the same or closely related epitope on 791T/36 monoclonal antibody as the human anti-iodiotypic antibody, has been produced. This antibody stimulates both cellular and humoral immune responses to human tumour cells. Furthermore the syngeneic responses are stronger than the xenogeneic immune responses. A clinical trial with the human monoclonal anti-idiotypic antibody in advanced colorectal cancer patients is now in progress and both cellular and humoral anti-tumour responses are monitored.