CUBAN MONOCLONAL ANTIBODIES FOR RADIOIMMUNODIAGNOSIS AND RADIOIMMUNOTHERAPY OF CANCER DISEASES

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The Centre of Molecular Immunology produces monoclonal antibodies for treating cancer diseases. We are mainly focus on two target systems; one is the epidermal growth factor receptor (EGF-R) because there is a tremendous relationship between the EGF/EGF-R system and several human tumours such as lung, head and neck, ovarian breast and brain cancers; the second one is the ganglioside system, the relevance of certain gangliosides in tumour growth and metastatic dissemination has been well documented, GM3(NeuGc) ganglioside is particularly interesting due to its restrictive expression in normal human tissues.

Nimotuzumab (h-R3) is a humanized monoclonal antibody (mAb) that was obtained by complementarity-determining regions grafting of a murine mAb (ior egf/r3) to a human framework having remarkable antiproliferative, pro-apoptotic, and antiangiogenic effects. A Phase I clinical trial was performed to evaluate the toxicity and clinical effect of an intracavitary (intracerebral) administration of a single dose of nimotuzumab (h-R3) labelled with increasing doses of ^{188}Re. All patients bearing astrocytomas grade III/IV should be treated previously with conventional therapies and have an EGF-R overexpression in the tumour, demonstrated by immunohistochemical study. Maximal tolerated dose was 3 mg of the h-R3 labelled with 10 mCi of ^{188}Re. The radioimmunoconjugate showed a high retention in the surgical created resection cavity and the brain adjacent tissues with a mean value of 85.5% of the injected dose one hour post-administration. This radioimmunoconjugate may be relatively safe and a promising therapeutic approach for treating high grade gliomas.

GM3(NeuGc) ganglioside is particularly interesting due to its restrictive expression in normal human tissues according to immunohistochemical studies, using either polyclonal or monoclonal antibodies. But both immunohistochemical and biochemical methods have strongly suggested its over-expression in human breast and colon tumours. Nevertheless, the lack of a direct evidence of this antigenic display in human cancers has kept the subject controversial. For the first time, we described herein the ‘‘in vivo’’ detection of GM3(NeuGc) ganglioside in human breast primary tumours using a radioimmunoscintigraphic technique with 14F7, a highly specific anti-GM3(NeuGc) ganglioside monoclonal antibody, labelled with 99mTc. In an open, prospective Phase I/II clinical trial, including women diagnosed in stage II breast cancer, the 14F7 monoclonal antibody accumulation in tumours at doses of 0.3 (n=5), 1 (n=5) and 3 mg (n=4) was evaluated. Noteworthy, the immunoscintigraphic study showed antibody accumulation in 100% of patients’ tumours for the 1 mg dose group. In turn, the radioimmunoconjugate injected at doses of 0.3 mg or 3 mg of the antibody, was uptaken by 60 and 33.3% of breast tumours, respectively. ‘‘In vivo’’ immune recognition of GM3(NeuGc) in breast tumours reinforces the value of this peculiar target for cancer immunotherapy. In two phase II Clinical Trials including women with metastatic breast cancer (n=14) and patients with colon cancer (n=19) in all stages, the 14F7 monoclonal antibody (3 mg) labelled with 99mTc (30-40 mCi) was also able to detect distant metastasis over expressing the GM3(NeuGc) ganglioside.