

PAG

A NEW DERIVATIVE FOR TARGETING CHLORAMBUCIL TO CANCER CELLS

M. Pagé and L.G. Bernier

Department of Biochemistry, Faculty of Medicine, Université Laval, Québec, Canada G1K 7P4.

The use of chlorambucil (CBL) in cancer chemotherapy is often limited because of undesirable side effects such as renal toxicity, bone marrow aplasia, pulmonary fibrosis and gastrointestinal disorders. In order to limit these systemic side effects, many authors have already coupled chlorambucil to various antibodies. Some conjugates were formed by physical adsorption or through the active moiety of the molecule leading to either toxicity or reduced activity. We report the covalent coupling of chlorambucil to antibodies using the isocyanate derivative of the drug. The specificity of the conjugates was tested using both anti-AFP and anti-CEA specific immunoglobulins on four different cell lines. The conjugates were found to be 3 to 30 times as active as the free drug on their respective targets. Studies involving various contact periods between the cells and the conjugates showed the avidity of the conjugates for their targets: the contact period could be reduced to 60 min to obtain full pharmacological activity.

PAG

TREATMENT OF HUMAN COLON ADENOCARCINOMA HETEROGRAFTED INTO NUDE MICE WITH ANTI-CEA-DAUNORUBICIN CONJUGATES

M. Pagé, F. Delorme¹, F. Lafontaine and L. DumasDepartment of Biochemistry, Faculty of Medicine, Université Laval, Québec, Canada G1K 7P4 and ¹Rhône-Poulenc Pharma Inc., Montréal, Canada.

Our laboratory has already demonstrated that daunorubicin, an anthracycline derivative, could be coupled to albumin or various specific antibodies while saving both the pharmacological and the immunological activity. Daunorubicin was conjugated to anti-carcinoembryonic antigen with glutaraldehyde in strictly controlled conditions to obtain about a 5:1 drug:protein ratio. When tested *in vitro* on CEA producing colon carcinoma cells (LoVo), the conjugate reduces the contact period needed to obtain full activity as compared to the free drug. Ten million LoVo cells were grafted s.c. into nu/nu mice for *in vivo* testing of the conjugate. Treatment was started when the tumour reached 4 mm in diameter by intraperitoneal injection of the free or conjugated drug (400 µg/kg/2 days) for 30 days. The conjugate was found to be efficient for limiting tumour growth as compared to the free daunorubicin or free antibody. Other experiments have shown that the conjugate was tolerated very well by animals.

Supported by Rhône-Poulenc Pharma Inc., Montréal, Canada.

PAG

MONOCLONAL ANTIBODIES TO HUMAN EMBRYONIC PREALBUMIN (EPA) AS A MARKER TO SARCOMAS

M. Pagé, C. Fortin and I. Dalifard¹Department of Biochemistry, Faculty of Medicine, Université Laval, Québec, Canada and ¹Centre Paul Papin, Angers, France.

Many human tumours are characterized by the production of oncofoetal antigens which may be used for the diagnosis and follow-up of cancer patients. Two of these antigens, alphafoetoprotein (AFP) and carcinoembryonic antigen (CEA) have been intensively investigated and they were found associated with carcinomas. Kalashnikov and Tatarinov have already described an oncofoetal protein of mesodermal origin, embryonic prealbumin, that they found associated with various sarcomas and soft tissue tumours. After purification of this protein from human amniotic fluid we have produced both polyclonal and monoclonal antibodies against EPA. Our rabbit antiserum cross-reacted with the original EPA. Polyclonal and monoclonal anti-EPA were found positive against various human cancer cell lines by indirect immunofluorescence and immunoperoxidase. Two normal cell lines were found to be negative. Monoclonal antibody E11 H11 3D1 was found to be positive on 11/13 deparaffinized sections of liposarcomas, chondrosarcomas and leiomyosarcomas; 4/4 rhabdomyosarcomas were negative; 1/1 liver angiosarcoma was found to be positive with G8 F22 2B3 monoclonal antibody while normal liver was negative. A RIA and an ELISA are now being developed for the measurement of this antigen in serum.

Supported by Cancer Research Society Inc., Montréal, Canada.
