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Immunotherapy with the Anti-EpCAM Monoclonal Antibody and Cytokines in Patients with Colorectal Cancer

A Clinical and Experimental Study

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Abstract

The tumor-associated antigen EpCAM (epithelial cell-adhesion molecule) (CO17-1A) is over expressed by various human carcinomas, including colorectal carcinoma (CRC). This antigen can be used as a target structure for specific immunotherapy with vaccines and monoclonal antibodies (MAb). Addition of cytokines to MAb therapy may augment immune effector functions and chemotherapeutic agents may also add to therapeutic efficacy.

In this thesis, we have analysed clinical and immunological responses of patients with advanced CRC treated with either the murine anti-EpCAM MAb (anti-EpCAM mMAb) or its chimeric counterpart (anti-EpCAM cMAb) in combination with cytokines and chemotherapeutics. Additionally, sequential analysis of cytokeratin positive (CK+) cells in the bone marrow (BM) were made in CRC patients receiving MAb based therapy for advanced disease or as adjuvant therapy.

Pretreatment natural killer (NK) cell cytotoxicity in vitro of peripheral blood mononuclear cells was an independent prognostic factor for overall survival and progression free survival (PFS) in patients receiving anti-EpCAM MAb based therapy as first-line therapy. The results from this study might be used for future patient selection and indicate that agents that activate NK cells should be considered to MAb-based treatment regimens.

The addition of GM-CSF, α-interferon and 5-fluorouracil to anti-EpCAM mMAb seemed to improved the antitumor response rate compared to historical control patients treated with anti-EpCAM mMAb alone (54% *v*s 15%) as well as PFS (15 *vs* 7 weeks). Clinical effects were mainly stable disease > 3months (11 of 14 responders) and responding patients survived longer than non-responders. The clinical efficacy of anti-EpCAM cMAb and GM-CSF was not better than in a historical control group who had received the anti-EpCAM mMAb and GM-CSF (overall response rates=21% *vs* 27%, respectively). Anti-idiotypic antibody (Ab2) concentrations as well as the frequency of patients mounting an Ab2-response in anti-EpCAM cMAb treated patients were lower as compared to anti-EpCAM mMAb-treated patients (69% *vs* 100%).

Following repeated daily subcutaneous (s.c.) injections of exogenous non-glycosylated *E.coli*-derived GM-CSF (molgramostim), the peak serum GM-CSF concentrations declined days 5 and 10 as compared to day 1. A dose-dependent increment in total white blood cell count was observed, the total numbers of GM-CSF receptor expressing cells increased during treatment while a transient decline in expression intensity was observed at day 5. The majority of patients developed binding but not neutralizing anti-GM-CSF antibodies. These results might support a receptor-mediated clearance of GM-CSF from the circulation. Importantly, high dose of GM-CSF resulted in lower antibody-dependent cellular cytotoxicity that may reflect immune suppression. Further studies are required to establish the optimal biological dose of different cytokines.

CK+ cells in BM were examined by immunohistochemistry on routinely processed BM clots, and CK+ cells were divided into different subtypes; Group A (CK+ probably malignant epithelial cells), Group B (CK+ morphologically non-epithelial cells) and Group C (CK+ contaminating cells). The presence of Group A cells did not adversely affect the prognosis while the presence of Group B cells probably indicates a poor prognosis in patients receiving adjuvant therapy. Sequential BM aspirations do not seem to add to the existing methods to follow the effect of treatment in CRC.

These results might provide further clinical studies with MAbs, combined with other agents with different modes of action to increase the clinical efficacy of MAb. Ideally, patients with a well preserved immune system and low or minimal tumor burden should be selected to MAb-based therapy.

Key words*:* Colorectal carcinoma, monoclonal antibodies, GM-CSF, pharmacokinetics, prognosis, bone marrow micrometastases, cytokeratin-positive cells

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